Archives of Neurology and Psychiatry

VOLUME 17 APRIL, 1927 NUMBER 4

# PROTEIN SENSITIZATION IN EPILEPSY

## A STUDY OF ONE THOUSAND CASES AND ONE HUNDRED NORMAL CONTROLS *

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Recently, much interest has centered in protein sensitization. This phenomenon, not yet fully understood, has been designated variously as "protein sensitization," "hypersensibility," "allergy" and "anaphylaxis." It has been invoked as a causative factor in a wide range of disease conditions of perplexing etiology, such as hay-fever, asthma, eczema and urticaria. One of the most recent conditions to be added to this constantly increasing group is epilepsy. We have considered the history of protein sensitization and the general bearing of the question of protein hypersensibility on convulsive disorders in a previous paper,[1] as part of a preliminary report on this subject.

### REVIEW OF THE LITERATURE

The development of the knowledge of protein sensitization, like much else that serum study has revealed during the last twenty-five years, takes root in isolated observations scattered through the early literature, but often regarded as merely noteworthy accidents or technical errors. The cutaneous reaction obtained by Jenner,[2] as early as 1789, may be regarded as the pioneer presentation of this theory. The earliest observation having a direct bearing on protein sensitization is one that

* Read at the Twenty-Fourth Annual Meeting of the National Association for the Study of Epilepsy, Richmond, Va., May 11 and 12, 1925.

1. Ward, J. F., and Patterson, H. A.: Protein Sensitization in Epilepsy: Preliminary Report, State Hosp. Quart. **10**:429 (May) 1925.

2. Jenner, E.: An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, particularly Gloucestershire, and Known by the Name of the Cow-Pox, London, S. Low, 1798.

Morgenroth [3] discovered in the writings of Magendie, published in 1839. In this, the latter describes the sudden death of dogs receiving repeated injections with egg albumin. A clear statement of the fundamental phenomenon was also given by Flexner,[4] in 1894, when he demonstrated that animals which had withstood one dose of dog serum would succumb to a much smaller, later dose, which was sublethal for a control animal not previously receiving injections. However, these isolated observations were neither correlated nor followed to their logical developments, and a systematic and purposeful study of the problem was deferred until Richet and Portier [5] attacked it in 1902. These investigators, whose work was foreshadowed by the earlier researches of Behring [6] and of Richet [7] and his previous collaborators, used a poisonous substance extracted from the tentacles of actinia, which they called actinocongestin. This substance, which is toxic per se, they injected into animals in sublethal doses and found that an animal so treated could be killed by a second injection of an amount too small to injure normal untreated animals. Richet's recognition of the distinct dependence of the hypersusceptible condition on a preceding inoculation with the same substance, and his conclusion that a definite incubation time must elapse after the first injection before susceptibility is developed, defined two of the most important criteria of this condition to which he gave the name of anaphylaxis (meaning "without shield"). On the other hand, the fact that Richet worked with primarily toxic substances delayed the final recognition of the general biologic significance of the anaphylactic phenomenon until a similar hypersensibility was noted in animals receiving injections with various substances which were in themselves harmless.

The discovery of Richet, however, initiated a wealth of purposeful and fruitful investigations in this field. In 1903, Arthus [8] found that rabbits would tolerate large amounts of horse serum which, when

3. Morgenroth: Ehrlich gesammelte Arbeiten, Trans., New York, Wiley and Son, 1906, p. 332, footnote.

4. Flexner, S.: The Pathologic Changes Caused by Certain So-Called Toxalbumins, M. News **65**:116, 1894.

5. Richet, C., and Portier: De l'action anaphylactique de certains venins, Compt. rend. Soc. de biol. **54**:170, 1902.

6. Von Behring, E., and Kitashiwa: Ueber Verminderung und Steigerung der ererbten Giftempfindlichkeit, Berl. klin. Wchnschr. **38**:157, 1901.

7. Hericourt and Richet, C.: Nouvelles expériences sur le traitement de la tuberculose expérimentale; injections d'eau iodée dans les poumons, Compt. rend. Soc. de biol. **5**:225, 1898.

8. Arthus, M.: Injections répétées de sérum de cheval chez le lapin, Compt. rend. Soc. de biol. **55**: 817, 1903.

administered by the usual routes as an initial dose, was entirely innocuous; but that subsequent smaller doses produced infiltration, edema, sterile abscesses and even gangrene at the point of subcutaneous injection. These conditions he recognized as a phenomenon of a systemic nature, which he regarded as analogous to the results obtained by Richet; he spoke of the hypersensitive rabbits as "anaphylactises" by a series of preparatory injections. Similar to that of Arthus is "the phenomenon of Theobald Smith" [9] who noticed, in 1904, that guinea-pigs used in the course of standardization of diphtheria antitoxin acquired progressively greater susceptibility to subsequent injections of horse serum.

A year afterward, Pirquet and Schick [10] undertook studies on the clinical manifestations of the injection of antitoxin and made an exhaustive study of the adverse effects so obtained in man, in whom the condition is usually known as serum sickness. Two years later, Pirquet [11] also introduced his cutaneous skin reaction for tuberculosis; this he interpreted in terms of his previous investigations in serum sickness and immediately classified as an allergic reaction, or a manifestation of anaphylaxis.

Meanwhile, with the observations of the last four authors cited as a point of departure, the problem was taken up, in 1905, by Otto [12] of the Frankfurt Institute of Experimental Therapy; he not only confirmed the observations of Arthus and Smith but also demonstrated that the Theobald Smith phenomenon was entirely independent of the toxin or antitoxin content of the injected serum, being produced by the injection of horse serum alone.

Almost simultaneously with Otto's publication, which appeared a little earlier than the first work of his contemporary American investigators, a study of the condition was presented by Rosenau and Anderson.[13] These authors showed that protein hypersusceptibility is

9. Smith, Theobald: The Pathologic Effects of Periodic Losses of Blood: An Experimental Study, J. M. Research **12**:385 (Oct.) 1904.

10. Von Pirquet, C., and Schick, B.: Die Serum Krankheiten, Leipzig and Vienna, F. Deuticke, 1905.

11. Von Piquet, C.: Demonstration zur Tuberkulindiagnose durch Hautimpfung, Berl. klin. Wchnschr. **44**:699, 1907.

12. Otto: Das Theobald Smithsche Phaenomen, von Leuthold's Gdnkschr. 1905, vol. 1; Ergänzungsband, 2, "Kolle u. Wassermann Handbuch," etc.

13. Rosenau, M. J., and Anderson, J. F.: A Study of the Cause of Sudden Death Following the Injection of Horse Serum, Marine Hosp. Serv. Hyg. Lab. Bull. no. 29, Washington, Government Printing Office, 1906; Studies on Hypersusceptibility and Immunity, ibid., no. 36, 1907; A New Toxic Action of Horse Serum, J. M. Research **15**:179, 1906; Further Studies on Hypersusceptibility and Immunity, ibid. **16**:381, 1907; The Specific Nature of Anaphylaxis, J. Infect. Dis. **4**:552, 1907; A Review of Anaphylaxis with Especial Reference to Immunity, ibid. **5**:85, 1908; A Stomach Lesion in Guinea-Pigs Caused by Diphtheria Toxin and Its Bearing on Experimental Gastric Ulcer, ibid. **4**:1, 1907.

not a transient condition but one of relatively long duration. They further found anaphylactic reactions to be specific in character; they discovered in addition that a single animal could be rendered sensitive at one and the same time to a number of different proteins. These proteins they also noted could be of plant, animal or bacterial origin, a fact subsequently confirmed by the studies of Vaughan and Wheeler,[14] Nicolle [15] and others. Rosenau and Anderson also demonstrated that the sensitive condition is transmitted from mother to offspring.

Attention was first called by Gay and Southard,[16] in 1909, to the characteristic picture found in an animal at necropsy performed immediately after death from anaphylaxis. They describe pulmonary emphysema as a constant feature and attribute anaphylactic death to intoxication of the respiratory center. The mechanism of respiratory death has been elaborated by Auer and Lewis [17] and confirmed by Biedl and Kraus,[18] who consider that anaphylactic death is due to tetanic spasm of the musculature of the small bronchi.

The mechanism of anaphylactic shock itself has been the subject of much speculation, and the literature abounds with discussions of Besredka,[19] Gay and Southard, Vaughan,[20] Coca,[21] Cooke [22] and a host of other writers. The earlier theories of Besredka and Gay and Southard

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14. Vaughan, V. C., and Wheeler, S. M.: The Effects of Egg White and Its Split Products on Animals; a Study of Susceptibility and Immunity, J. Infect. Dis. **4**:476, 1907.

15. Nicolle: Les colorations vitales des microbes, Bull. de l'Inst. Pasteur **1**:137, 1903.

16. Gay, F. P., and Southard, E. E.: On Serum and Anaphylaxis in the Guinea-Pig, J. M. Research **16**:143, 1907; Further Studies in Anaphylaxis: II. On Recurrent Anaphylaxis and Repeated Intoxication in Guinea-Pigs by Means of Horse Serum, ibid. **19**:1, 1908; Further Studies in Anaphylaxis: III. The Relative Specificity of Anaphylaxis, ibid. **19**:5, 1908; Further Studies in Anaphylaxis: IV. The Localization of Cell and Tissue Anaphylaxis in the Guinea-Pig with Observations on the Cause of Death in Serum Intoxication, ibid. **19**:17, 1908.

17. Auer, J., and Lewis, P. A.: Acute Anaphylaxis Death in Guinea-Pigs: Its Cause and Possible Prevention, J. A. M. A. **53**:458 (Aug. 7) 1909; The Physiology of the Immediate Reaction of Anaphylaxis in the Guinea-Pig, J. Exper. Med. **12**:151, 1910.

18. Biedl, A., and Kraus, R.: Ueber passive Anaphylaxie (Serumanaphylaxie), Ztschr. f. Immunitätsforsch. u. exper. Therap. **4**:115, 1909-1910; Experimentelle Studien über Anaphylaxie, Wien. klin. Wchnschr. **23**:38, 1910; Die Wirkung intravenös injizierten Peptons beim Meerschweinchen, Zentralbl. f. Physiol. **24**:258, 1910.

19. Besredka: Toxicité des sérums thérapeutiques: sa variabilité et son dosage, Ann. de l'inst. Pasteur. **21**:777, 1907; Comment peut-on combattre l'anaphylaxie? ibid. **21**:950, 1907; Du mécanisme de l'anaphylaxie vis-à-vis du serum de cheval, ibid. **22**:496, 1908; De l'anaphylaxie: 6. Mémoire de l'anaphylaxie lactique, ibid. **23**:166, 1909; De l'anaphylaxie sérique expérimentale, Bull. de l'Inst. Pasteur **6**:841, 889 and 937, 1908; Du traitement préventif de l'anaphylaxie (anti-anaphylaxie), ibid. **7**:721, 1909; De la vaccination anti-

have proved of little importance in the actual understanding of the phenomenon. Vaughan and Wheeler's [23] theory of the toxicity of protein cleavage products is well known. An interesting conception is that of Friedberger,[24] who regards anaphylactic shock as the result of an interaction between the offending protein and a substance, called an anaphylatoxin, formed by the previous reaction between the initial sensitizing dose of the protein and the normal complement of the blood serum. In this connection, Novy and De Kruif point out that it is important to realize from the medical point of view that the blood of an animal may be abnormally toxic owing to the presence of anaphylatoxin developed in the animal through some unrecognized cause that may lie in peculiarity of diet, exposure, or in obscure infection, etc. The profusion of different theories indicates clearly that the underlying principle of protein sensitization is not known.

Anaphylaxis in man, however, seldom appears in the extreme degree of severity in which it is manifested in the lower animals. Consequently, the conclusions of Van Leeuwen and Zeydner [25] are of interest in connection with the employment of terms interchangeably in referring to this diathesis. These writers believe that the designation of the allergic condition described by Coca, Cooke and others as anaphylactic should be abandoned. While the allergic state as it occurs in man is probably related to anaphylaxis, it is usually not the same type of anaphylactic phenomenon that is encountered in animal experimentation.

The rôle of heredity in protein sensitization in man is also somewhat in dispute. Baker [26] found the incidence of protein sensitization in

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anaphylactique, Compt. rend. Soc. de biol. **65**:478, 1908; Du moyen d'empêcher la mort subite produite par injections répétées du sang ou des microbes dans la circulation générale, ibid. **67**:266, 1909.

20. Vaughan, V. C.: A Contribution to the Chemistry of the Bacterial Cell and a Study of Some of the Split Products on Animals, Boston M. & S. J. **155**:215 and 243, 1906; Vaughan, V. C.; Vaughan, V. C., Jr., and Vaughan, J. W.: Protein Split Products in Relation to Immunity and Disease, Philadelphia, Lea & Febiger, 1913, p. 139.

21. Coca, A. F.: The Site of Reaction in Anaphylactic Shock, Ztschr. f. Immunitätsforsch. u. exper. Therap. **20**:623, 1914.

22. Cooke, R. A.: Protein Sensitization in the Human, M. Clin. N. Amer. **1**:721 (Nov.) 1917.

23. Vaughan, V. C.: The Action of the Intracellular Poisons of the Colon Bacillus, J. A. M. A. **44**:1340 (April 29) 1905.

24. Friedberger, E., and Hartoch, O.: Ueber das Verhalten des Komplements bei der aktiven und passiven Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:581, 1909.

25. Storm van Leeuwen, W., and Zeydner: On the Occurrence of a Toxic Substance in the Blood in Cases of Bronchial Asthma, Urticaria, Epilepsy, and Migraine, Brit. J. Exper. Path. **3**:282 (Dec.) 1922.

26. Baker, H. M.: Incidence of Protein Sensitization in the Normal Child, Am. J. Dis. Child. **19**:114 (Feb.) 1920.

the normal child practically negligible. On the other hand, Cooke and Van der Veer [27] regard inheritance as an important factor in allergic diseases, having reported, in 1916, that the antecedents of 48 per cent of 504 patients with hay-fever had suffered from this condition. Brown [28] likewise considers the hereditary element as important, believing that the inability to metabolize properly is more noticeable in some families than in others. In the latter's opinion, this hereditary factor evidences itself not in transmission of the disease per se but in the inheritance of certain chemical predispositions that result in incapacity to digest the protein properly.

Protein sensitization in man, according to the majority of writers, is indicated in an intolerance for a certain definite protein such as food, animal emanations, dandruff, feathers or pollens; this is due to previous sensitization with the offending material. Such disturbances of protein metabolism may manifest themselves in various organs of the body, either singly or jointly, in the latter case exemplifying what is known as a syndrome. The sources of protein intoxication may be traced not alone to the poisoning resulting from the ingestion of foods—animal or vegetable—but also to pollens, emanations and even to various forms of bacteria entering through either the respiratory or the alimentary systems. Thus, conditions that are considered manifestations of this disturbed metabolism include asthma, hay-fever, whooping cough, influenza, eczema, urticaria, angioneurotic edema, intestinal disturbances, bladder pain (Duke), renal conditions and a number of others among which are included various disturbances hitherto considered as of unknown etiology. These sometimes embrace arterial and cardiovascular conditions, those of autointoxication and malnutrition, and even the arthritides and some neurasthenic and psychasthenic states.

The theory that food poisons or food susceptibility may be responsible for a certain type of epilepsy has already been advanced. In considering the possibility that this pathologic susceptibility may manifest itself in organs other than those that come in direct contact with the foreign protein, the following statement of Duke [29] is of interest:

> The tissues most commonly affected by allergy are those which come in contact most frequently with foreign substances that tend to sensitize; namely, the mucous membranes of the eye, nose, pharynx and bronchial tubes, less often the skin and the mucous membranes of the alimentary tract and, much less often, internal organs, as the bladder. However, symptoms may be manifest solely in

27. Cooke, R. A., and Van der Veer, A., Jr.: Human Sensitization, J. Immunol. **1**:201 (June) 1916.

28. Brown: M. Press & Circ. **106**:345 (Nov. 6) 1918.

29. Duke, W. W.: Food Allergy as a Cause of Bladder Pain, Ann. Clin. Med. **1**:117 (Sept.) 1922; Specific Hypersensitiveness as a Common Cause of Illness, ibid. **1**:178 (Nov.) 1922.

remote organs while the tissue at the primary portal of entry may show little or no reaction. For example, asthma or eczema may be a result of the ingestion of milk or egg; conversely, dyspepsia and abdominal pain may follow subcutaneous injection of pollen extract or egg albumin.

Thus, it is logical to anticipate evidences of protein sensitization in almost any organ of the body.

A local inflammatory reaction resulting from contact with a specific protein may be explained on the ground that the protein in the body is set free in the superficial capillaries of the skin, as evidenced by areas of congestion that are followed by an acute edema with serous exudation producing an urticarial wheal. That the same condition may occur in the brain or meninges of an individual sensitive to a particular protein seems, therefore, to be a reasonable hypothesis. Edema may take place in the brain or meninges in response to a state of allergic sensitization, and produce the symptoms of epilepsy. Since it is admitted that protein sensitization frequently manifests itself as asthma in the lung tissue, as hay-fever in the nasal tissue and as eczema and urticaria in the skin, is it not also probable that it may manifest itself in the brain by calling forth the syndrome of epilepsy?

At this point, it is interesting to recall the work of Besredka and Steinhardt,[30] whose studies led them to the conclusion that the most effectual and rapid method of producing anaphylactic shock in animals consisted of direct injection into the brain. Curiously, however, while these two investigators obtained violent reactions by the injection of the second or toxicogenic dose into the brain, they were unable to bring about sensitization by this path with doses that were sufficient to sensitize the animal by the intravenous method of administration. Rosenau and Anderson repeated this work and obtained similar results with small amounts of protein, finding that intracerebral sensitization could be accomplished with doses of 0.0001 cc. or more. According to these authors, animals sensitized intracerebrally became anaphylactic more readily than those receiving subcutaneous injections.

In regard to man, Miller [31] points out certain facts that suggest a possible relationship between epilepsy and protein sensitization. Tinel [32] refers to the disappearance of epileptic seizures after attacks of typhoid fever and pneumonia, Spratling [33] reported that epileptic patients who

30. Besredka, A., and Steinhardt, E.: De l'anaphylaxie et de l'anti-anaphylaxie vis-à-vis du sérum de cheval, Ann. de l'Inst. Pasteur **21**:117, 1907; Du mécanisme de l'anti-anaphylaxie, ibid. **21**:384, 1907.

31. Miller, J. L.: Evidence that Idiopathic Epilepsy is a Sensitization Disease, Am. J. M. Sc. **168**:635 (Nov.) 1924.

32. Tinel, J.: New Conceptions of Epilepsy, Médecine **3**:366 (Feb.) 1922.

33. Spratling, W. P.: Epilepsy and Its Treatment, Philadelphia and New York, W. B. Saunders Company, 1904.

acquired tuberculosis frequently show amelioration or disappearance of seizures. Turnowsky [34] refers to three cases of established epilepsy in which the seizures subsided in two after pneumonia and in one after scarlatina. Hamilton [35] reports the cases of twelve epileptic patients who acquired typhoid; nine showed distinct improvement—one of these was free from seizures after four years. This improvement after infection might be explained on the basis of desensitization, as this is the accepted explanation in asthma.

Again, pregnancy not infrequently modifies epilepsy; the attacks may subside temporarily during this period or may first develop at this time. Weir Mitchell [36] reported that he had never seen epilepsy made worse by pregnancy; on the other hand, seizures are often less frequent. Beraud observed the effect of pregnancy on thirty-one epileptic patients: eight were influenced unfavorably and fifteen favorably, in eight of whom the seizures entirely disappeared during this period. Since the placenta behaves as a foreign protein to the mother, it is possible that desensitization might have taken place.

This evidence is merely suggestive that epilepsy may be a sensitization disease. However, there is considerable therapeutic evidence to support this view. It has been reported by French physicians that after treatment for rabies, or after the use of diphtheria antitoxin, epileptic seizures have disappeared temporarily. Bouché and Hustin,[37] following this lead, treated a number of epileptic patients with normal horse serum, with encouraging results. In 1908, Spangler [38] reported the use of snake venom in the treatment of thirty-six cases of epilepsy in which crotalin was injected subcutaneously. He reported that every patient was affected favorably; in some instances the improvement was slight, while in others the seizures became infrequent or the major attacks disappeared entirely. At the time the article was written, three patients had been entirely free from seizures for two years or more and two for eighteen months. Snake venom contains both a poisonous peptone and a globulin. The peptone is largely a nerve poison; the globulin lessens tissue coagulability and increases vessel permeability. As there was a theory current at the time of Spangler's publication that the epileptic seizure is associated with increased coagulability, he ascribed his good results to modification of blood coagulation. It is not impossible that the thera-

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34. Turnowsky, M.: Drei Fälle von vollständig geheilter Epilepsie, Wien. med. Wchnschr. **51**:1621, 1901.

35. Hamilton, A. S.: The Effect of Intercurrent Disorders on Preexisting Epilepsy, J. A. M. A. **53**:1902 (Dec. 4) 1909.

36. Mitchell, S. Weir, quoted by Hamilton (footnote 35).

37. Bouché and Hustin, quoted by Tinel (footnote 32).

38. Spangler, R. H.: The Crotalin Treatment of Epilepsy; Chemical Composition of Snake Venom; Its Possible Effect on Blood Coagulation; Report of Eight Cases, New York M. J. **96**:520, 1912.

peutic effect observed may have been due to protein densitization. Spangler's treatment appeared so irrational that no attempt was made in this country to verify his results. In France, however, reports have appeared from time to time recording the value of the treatment. In 1911, Lion [39] reported good results in epilepsy from injections of brain extract and, in 1920, Held [40] reported 400 cases of epilepsy in which the patients received the serum of animals previously injected with serum and spinal fluid from epileptic patients. He states that 18 per cent of his patients have been free from seizures for from two to four years, and only 30 per cent were not benefited. Miller believes that if there is any value in this treatment it is probably due to the effect of normal serum rather than to changes produced by previous treatment of the animals. In 1921, James Crocket,[41] an English physician conducting a tuberculosis sanatorium in which all patients received tuberculin, observed that when the patient in addition had epilepsy the seizures usually disappeared. He then treated twenty-three epileptic patients with injections of tuberculin. At the time of his report eleven of these had been free from seizures for three months or more. One patient in this group, who had had 309 major and minor seizures during the month preceding the treatment, had been entirely free from seizures for nine months. According to Miller, all the foregoing methods of treatment can be classed properly as protein therapy, but whether the results were due to nonspecific desensitization or to some other action of protein is a matter to be determined.

The work of Van Leeuwen and Zeydner furnishes some additional support to the sensitization theory. Using a method first proposed by Freund for isolating a muscle stimulating substance from the blood, they were unable to detect this substance in the blood of normal individuals. They then attempted to isolate it from the blood of patients suffering with a variety of diseases and found it present only in the blood of patients with asthma, urticaria, migraine and epilepsy. It is their opinion that this toxic substance is in some way related to the allergic disposition of these patients. In this connection Miller inclines to the view that if these results are confirmed, it would at least indicate a close relationship between the diseases in this group.

Before any statements of a more specific nature are attempted, it must be understood that the considerations here brought forth are not to be construed as necessarily applicable to all cases of epilepsy. The etiology of the various conditions sometimes attributed to anaphylaxis

39. Lion, M. D.: Specific Treatment of Epilepsy, Vrach. Gaz. **17**:1542, 1910.

40. Held, W.: Die neue Serumtherapie der Epilepsie, Neurol. Centralbl. **39**:594 (Sept. 16) 1920.

41. Crocket, James: Tuberculin in Epilepsy, Brit. M. J. **1**:458 (March 26) 1921.

may be different in different instances. For example, it is well known that all forms of asthma cannot be traced to the same origin.

The possible relation between food poisoning and epilepsy has already been mentioned by a number of authors. Spratling, in 1904, wrote: "Individual susceptibility to certain foods, harmless in themselves, but poisonous to others should not be overlooked; such foods usually consist of shellfish and certain fruits including peaches and strawberries." Wechsler,[42] in 1921, in a study of a series of fifty-eight cases, expressed a firm convicion that certain foodstuffs bear a special relation to some types of epilepsy, but confessed himself unable to prove his belief. In the same year, Thomson,[43] of Edinburgh, reporting 200 cases of convulsions in infants, laid special stress on the possible relation between poisoning from common foodstuffs and the idiopathic convulsions of infancy, and expressed the opinion that there can be little doubt that the interesting and as yet only partially understood process of anaphylaxis plays an essential part in the causation of some and perhaps many morbid phenomena. Neither Wechsler's nor Thompson's patients were given skin tests, however. In a paper written in 1922, one of us [44] suggested protein sensitization as a possible cause of epilepsy, and presented (in addition to the authors just cited) reports of two cases of Bell [45] in which the patients' skin had been tested for certain foods, but not for bacterial protein; these cases were considered controllable as long as hypersensitive food proteins were eliminated from the diet. A little later, Howell [46] contributed an intimate study, begun in August, 1921, of fourteen epileptic children. Skin tests were made on eleven of these for both bacterial and food proteins; the remaining three were tested for food proteins alone. All except one were sensitive to one or more foodstuffs, and some of these were also sensitive to bacterial protein. In the single exception, however, the child was sensitive to bacterial protein alone. From England, Wallis and Nicol [47] reported, in 1923, the results of skin tests for various food proteins on 128 persons (sixty-eight females and fifty-four males). Of these, forty-six (twenty-eight females and eighteen males) gave positive reactions to different proteins, while

42. Wechsler, I. S.: Treatment of Epilepsy, Based on Records of Fifty-Eight Cases, M. Rec. **100**:714 (Oct. 22) 1921.

43. Thomson, J.: Clinical Types of Convulsive Seizures in Very Young Babies, Brit. M. J. **2**:679 (Oct. 29) 1921.

44. Ward, J. F.: Protein Sensitization as Possible Cause of Epilepsy and Cancer, New York M. J. **115**:592 (May 17) 1922.

45. Personal communication to the authors.

46. Howell, L. P.: Differentiation of Skin Eruptions in New-Born, Ohio State M. J. **19**:417 (June) 1923.

47. Wallis, R. L. M.; Nicol, W. D., and Craig, M.: Importance of Protein Hypersensitivity in Diagnosis and Treatment of Special Group of Epileptics, Lancet **1**:741 (April 14) 1923.

seventy-six (forty females and thirty-six males) did not react at all. McCready and Ray,[48] in October, 1924, cited seven cases of convulsive disorder in which the condition is considered as related to protein sensitization. In one of these tobacco is regarded as the offending protein, while in another vaccination material is accused. These sporadic references in the literature indicate the possible relation between protein hypersensibility and convulsions, and the earlier ones provided the stimulus for the investigation reported in this paper.

## MATERIAL STUDIES AND TECHNIC

In this investigation, 1,000 epileptic patients were tested by the cutaneous method for evidences of protein hypersensibility. Of this number 500 were patients at Craig Colony and 500 were inmates of the New Jersey State Village for Epileptics. The former group was composed of an equal number of carefully selected cases of both sexes, chosen because of the apparent absence of any organic etiologic factor, while the latter group consisted chiefly of males, although a fair number of females were included. As a check on the results obtained, 100 voluntary nonepileptic controls were similarly tested.

TABLE 1.—*Cases Studied at Craig Colony*

| | Male | Female |
|---|---|---|
| Number of cases examined | 250 | 250 |
| Number not reacting | 156 | 159 |
| Number reacting | 94 | 91 |
| Percentage reacting | 37.6 | 36.4 |

The skin tests were made in the following manner:

The forearm was cleansed with warm water and gently dried with a soft towel. When it was thoroughly dry, the tests were begun near the elbow and continued down the forearm in a parallel series extending from right to left. For each test a small, superficial incision was made in the outer layer of the skin. In scarifying, it is necessary to avoid drawing blood or even excess lymph, as the body fluids wash away the protein extract and interfere with the reaction. A small quantity of known pure protein extract was then applied to the wound, moistened with a little decinormal sodium hydroxide solution, and was worked gently into the abrasion with a sterile toothpick. After half an hour's application, the material was gently washed away with warm water. In doing this, care was taken to avoid irritating the skin in case a pseudoreaction should be excited. A reading was made immediately after cleansing. The second corroborating reading after a lapse of twenty-four hours, mentioned in our preliminary report, was omitted here, since further experience had shown that it provided no additional information of value. In a few instances in which the results obtained by the cutaneous method were uncertain, recourse was taken to intradermal injection

48. McCready, E. B., and Ray, H. M.: Allergy as Factor in Etiology of Idiopathic Epilepsy, M. J. & Rec. (supp.) **120**:117 (Oct. 15) 1924.

TABLE 2.—*Reactions to Each Protein at Craig Colony* *

| Protein | Males | | | | | | | | Females | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Plus Minus | | One Plus | | Two Plus | | Four Plus | | Plus Minus | | One Plus | | Two Plus | | Four Plus | |
| | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| Apple | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Asparagus | 3 | 0.501 | 1 | 0.334 | .. | ..... | .. | ..... | 16 | 2.675 | 2 | 0.334 | .. | ..... | .. | ..... |
| Banana | 4 | 0.668 | 2 | 0.334 | .. | ..... | .. | ..... | 18 | 3.010 | 3 | 0.501 | .. | ..... | .. | ..... |
| Barley | 10 | 1.672 | 6 | 1.003 | 4 | 0.668 | .. | ..... | 11 | 1.839 | 2 | 0.334 | .. | ..... | 1 | 0.167 |
| Bean | 4 | 0.668 | 2 | 0.334 | 2 | 0.334 | .. | ..... | 7 | 1.020 | 1 | 0.167 | .. | ..... | .. | ..... |
| Beef | 2 | 0.334 | 1 | 0.167 | .. | ..... | .. | ..... | 6 | 1.003 | .. | ..... | .. | ..... | .. | ..... |
| Beet | 6 | 1.003 | 3 | 0.501 | .. | ..... | .. | ..... | 9 | 1.505 | 2 | 0.334 | .. | ..... | .. | ..... |
| Buckwheat | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... |
| Cabbage | 5 | 0.836 | 3 | 0.501 | .. | ..... | .. | ..... | 7 | 1.020 | 1 | 0.167 | .. | ..... | .. | ..... |
| Cantaloupe | 4 | 0.668 | 2 | 0.334 | .. | ..... | .. | ..... | 3 | 0.501 | 2 | 0.334 | .. | ..... | .. | ..... |
| Carrot | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... |
| Casein | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Cauliflower | 3 | 0.501 | 2 | 0.334 | .. | ..... | .. | ..... | 6 | 1.003 | .. | ..... | .. | ..... | .. | ..... |
| Celery | 1 | 0.167 | 2 | 0.334 | .. | ..... | .. | ..... | 5 | 0.836 | 1 | 0.167 | .. | ..... | .. | ..... |
| Cheese | 4 | 0.668 | 1 | 0.167 | .. | ..... | .. | ..... | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... |
| Cherry | 1 | 0.167 | 1 | 0.167 | 1 | 0.167 | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Chicken | 1 | 0.167 | 4 | 0.668 | 1 | 0.167 | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |
| Cocoa | 5 | 0.836 | 3 | 0.501 | .. | ..... | .. | ..... | 4 | 0.668 | 1 | 0.167 | .. | ..... | .. | ..... |
| Codfish | .. | ..... | .. | ..... | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Coffee | 3 | 0.501 | 1 | 0.167 | .. | ..... | .. | ..... | 4 | 0.668 | .. | ..... | .. | ..... | .. | ..... |
| Corn | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Cucumber | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Eggplant | 3 | 0.501 | 2 | 0.334 | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Egg white | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Egg yolk | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... |
| Ginger | 4 | 0.668 | 1 | 0.167 | .. | ..... | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |

* The same proteins used in this group were used for the controls.

* The same proteins used in this group were used for the controls.

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Grape | 2 | 0.334 | 2 | 0.334 | .. | ..... | .. | ..... | 4 | 0.668 | 1 | 0.167 | .. | ..... | .. | ..... |
| Lactalbumin | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Lamb | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... |
| Lettuce | 4 | 0.668 | 4 | 0.668 | .. | ..... | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |
| Lima bean | 4 | 0.668 | .. | ..... | .. | ..... | .. | ..... | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... |
| Mackerel | 4 | 0.668 | 1 | 0.167 | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Milk (cow) | 7 | 1.020 | 2 | 0.334 | .. | ..... | .. | ..... | 4 | 0.668 | .. | ..... | .. | ..... | .. | ..... |
| Oat | 5 | 0.836 | 2 | 0.334 | .. | ..... | .. | ..... | 12 | 2.006 | 1 | 0.167 | .. | ..... | .. | ..... |
| Onion | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... | 13 | 2.173 | .. | ..... | .. | ..... | .. | ..... |
| Orange | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... |
| Oyster | 2 | 0.334 | .. | ..... | 2 | 0.334 | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Parsnip | 2 | 0.334 | 1 | 0.167 | .. | ..... | .. | ..... | 4 | 0.668 | .. | ..... | .. | ..... | .. | ..... |
| Pea | 4 | 0.668 | 2 | 0.334 | .. | ..... | 1 | 0.167 | 6 | 1.003 | .. | ..... | .. | ..... | .. | ..... |
| Peach | 2 | 0.334 | 2 | 0.334 | .. | ..... | .. | ..... | 8 | 1.337 | .. | ..... | 1 | 0.167 | .. | ..... |
| Pear | 1 | 0.167 | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... |
| Pepper (B) | 9 | 0.505 | 3 | 0.501 | .. | ..... | .. | ..... | 10 | 1.672 | 5 | 0.836 | .. | ..... | .. | ..... |
| Pineapple | 10 | 1.672 | .. | ..... | .. | ..... | .. | ..... | 7 | 1.020 | .. | ..... | .. | ..... | .. | ..... |
| Plum | 6 | 1.003 | 3 | 0.501 | .. | ..... | .. | ..... | 6 | 1.003 | .. | ..... | .. | ..... | .. | ..... |
| Pork | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... | 6 | 1.003 | .. | ..... | .. | ..... | .. | ..... |
| Potato | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... | 3 | 0.501 | .. | ..... | .. | ..... |
| Prune | 2 | 0.334 | 3 | 0.501 | .. | ..... | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |
| Rhubarb | 3 | 0.501 | .. | ..... | .. | ..... | .. | ..... | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... |
| Rice | 1 | 0.167 | 4 | 0.668 | .. | ..... | .. | ..... | 3 | 0.501 | 2 | 0.334 | .. | ..... | .. | ..... |
| Salmon | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | 2 | 0.334 | 1 | 0.167 | .. | ..... | .. | ..... |
| Spinach | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... |
| Squash | 2 | 0.334 | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... | .. | ..... |
| Strawberry | 5 | 0.836 | .. | ..... | .. | ..... | .. | ..... | 6 | 1.003 | 1 | 0.167 | .. | ..... | .. | ..... |
| String bean | 4 | 0.668 | 4 | 0.668 | .. | ..... | .. | ..... | 8 | 1.337 | 1 | 0.167 | .. | ..... | .. | ..... |
| Tea | 6 | 1.003 | 1 | 0.167 | .. | ..... | .. | ..... | 9 | 1.505 | 3 | 0.501 | .. | ..... | .. | ..... |
| Tobacco | 1 | 0.167 | 4 | 0.668 | .. | ..... | .. | ..... | 1 | 0.167 | 1 | 0.167 | .. | ..... | .. | ..... |
| Tomato | 3 | 0.501 | 1 | 0.167 | 1 | 0.167 | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |
| Turnip | 4 | 0.668 | 3 | 0.501 | .. | ..... | .. | ..... | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... |
| Veal | 1 | 0.167 | .. | ..... | .. | ..... | .. | ..... | 2 | 0.334 | .. | ..... | .. | ..... | .. | ..... |
| Wheat (whole) | 2 | 0.334 | 1 | 0.167 | .. | ..... | .. | ..... | 6 | 1.003 | .. | ..... | 1 | 0.167 | .. | ..... |
| Total | 175 | | 98 | | 12 | | 1 | | 274 | | 35 | | 2 | | 1 | |

to confirm the doubtful readings. Sixty different individual proteins were used for the Craig Colony group and for the controls, and seventy-two for the New Jersey State Village group.

As already indicated, the 500 patients from Craig Colony included 250 males and 250 females. Of the former, 156 gave negative reactions and ninety-four, or 37.6 per cent, gave positive reactions of varying degrees of intensity; of the latter, 159 were negative and ninety-one, or 36.4 per cent, showed positive reactions also of varying degrees of intensity. It is interesting to note in passing how closely the results obtained in the two sexes approached one another. The number and the percentage of reactions obtained with each protein used are given in tables 1 and 2. The kind and number of protein extracts employed are indicated in table 2.

On the average, exactly 37 per cent of these patients gave a positive reaction, sometimes, however, a rather weak one. In these reactors, the chief offending proteins were: among the males barley, black pepper and pineapples; among the females bananas, asparagus and black pepper, in the order named. In this connection, it may be remarked that the proteins showing the greatest number of positive reactions are not the same ones that gave the highest readings in our preliminary report of 100 cases; but this fact is not particularly significant, since sensitization to different proteins naturally may vary greatly with different persons.

The group from the New Jersey State Village for Epileptics consisted of 342 males and 158 females. Among the former 164 were found by one of us (J. F. W.) to give a negative reaction and 178, or 52 per cent, a positive one; among the latter, fifty-two reactions were regarded as negative and 106, or 67 per cent, as positive. The number of reactions obtained in this group with each protein in both sexes and the percentage of reactions secured with each protein appear in table 3. The kind and variety of protein extracts used here may be ascertained from either table.

Of the New Jersey State Village patients, 56.8 per cent manifested protein hypersensitivity. The proteins reacting with greatest frequency were, successively, mustard, cheese, veal, orris root and white potato. The relative number of positive reactions in this group exceeds those obtained even in the preliminary study previously mentioned. The reason for the comparatively high percentage of reactions manifested here is not apparent.

The control group was composed of 100 nonepileptic persons, chiefly females, who voluntarily offered themselves as subjects in order that the results obtained might be checked. The readings given by these patients is shown in table 4.

Among the 100 controls, eight persons were found who gave eleven positive reactions of varying degrees of intensity. Several of these

TABLE 3.—*Reactions to Each Protein at the New Jersey State Village for Epileptics*

| Protein | Plus Minus | | One Plus | | Two Plus | | Three Plus | | Total Reactions |
|---|---|---|---|---|---|---|---|---|---|
| | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent | |
| Apple | 4 | 0.8 | 1 | 0.2 | .. | ... | .. | ... | 5 |
| Asparagus | 7 | 1.4 | 7 | 1.4 | .. | ... | .. | ... | 14 |
| Banana | 5 | 1.0 | 5 | 1.0 | .. | ... | .. | ... | 10 |
| Barley | 4 | 0.8 | 7 | 1.4 | 4 | 0.8 | 2 | 0.4 | 17 |
| Bean, lima | 6 | 1.2 | 10 | 2.0 | .. | ... | .. | ... | 16 |
| Bean, navy | 2 | 0.4 | 5 | 1.0 | 1 | 0.2 | .. | ... | 8 |
| Bean, string | .. | ... | .. | ... | .. | ... | .. | ... | .. |
| Beef | 3 | 0.6 | 5 | 1.0 | .. | ... | .. | ... | 8 |
| Beet | 3 | 0.6 | 3 | 0.6 | .. | ... | .. | ... | 6 |
| Buckwheat | 9 | 1.8 | 10 | 2.0 | 2 | 0.4 | .. | ... | 21 |
| Cabbage | 4 | 0.8 | 3 | 0.6 | .. | ... | .. | ... | 7 |
| Cantaloupe | 2 | 0.4 | 2 | 0.4 | 1 | 0.2 | .. | ... | 5 |
| Carrot | 5 | 1.0 | 1 | 0.2 | .. | ... | .. | ... | 6 |
| Casein | 9 | 1.8 | 7 | 1.4 | 1 | 0.2 | .. | ... | 17 |
| Cat hair | .. | ... | 2 | 0.4 | .. | ... | .. | ... | 2 |
| Cauliflower | 12 | 2.4 | 7 | 1.4 | 1 | 0.2 | .. | ... | 20 |
| Celery | 6 | 1.2 | 6 | 1.2 | 1 | 0.2 | .. | ... | 13 |
| Cheese | 14 | 2.8 | 10 | 2.0 | .. | ... | .. | ... | 24 |
| Cherry | 5 | 1.0 | 5 | 1.0 | 1 | 0.2 | .. | ... | 11 |
| Chicken | 4 | 0.8 | 8 | 1.6 | .. | ... | .. | ... | 12 |
| Cocoa | 3 | 0.6 | 3 | 0.6 | .. | ... | .. | ... | 6 |
| Cod | 12 | 2.4 | 5 | 1.0 | 1 | 0.2 | .. | ... | 18 |
| Coffee | 6 | 1.2 | 8 | 1.6 | .. | ... | .. | ... | 14 |
| Corn | .. | ... | 4 | 0.8 | 6 | 1.2 | .. | ... | 10 |
| Cucumber | 12 | 2.4 | 5 | 1.0 | .. | ... | .. | ... | 17 |
| Eggplant | 6 | 1.2 | 13 | 2.6 | 1 | 0.2 | .. | ... | 20 |
| Egg, whole | 6 | 1.2 | 5 | 1.0 | .. | ... | .. | ... | 11 |
| Egg, yolk | 10 | 2.0 | 2 | 0.4 | .. | ... | .. | ... | 12 |
| Feathers, chicken | 2 | 0.4 | 6 | 1.2 | .. | ... | .. | ... | 8 |
| Feathers, duck | .. | ... | .. | ... | .. | ... | .. | ... | .. |
| Feathers, goose | .. | ... | .. | ... | .. | ... | .. | ... | .. |
| Ginger | 11 | 2.2 | 4 | 0.8 | .. | ... | .. | ... | 15 |
| Gliadin | 6 | 1.2 | 12 | 2.4 | .. | ... | .. | ... | 18 |
| Globulin | 14 | 2.8 | 7 | 1.4 | .. | ... | .. | ... | 21 |
| Glutinin | 5 | 1.0 | 10 | 2.0 | .. | ... | .. | ... | 15 |
| Grape | 7 | 1.4 | 9 | 1.8 | .. | ... | .. | ... | 16 |
| Horse hair | 12 | 2.4 | 3 | 0.6 | .. | ... | .. | ... | 15 |
| Lactalbumin | 10 | 2.0 | 7 | 1.4 | .. | ... | .. | ... | 17 |
| Lamb | 5 | 1.0 | 2 | 0.4 | .. | ... | .. | ... | 7 |
| Lettuce | 3 | 0.6 | 9 | 1.8 | 1 | 0.2 | .. | ... | 13 |
| Leucosin | 5 | 1.0 | 5 | 1.0 | 1 | 0.2 | .. | ... | 11 |
| Mackerel | 9 | 1.8 | 5 | 1.0 | 2 | 0.4 | .. | ... | 16 |
| Milk, cow | 10 | 2.0 | 5 | 1.0 | .. | ... | 1 | 0.2 | 15 |
| Mustard | 6 | 1.2 | 18 | 3.6 | .. | ... | .. | ... | 25 |
| Oat | 10 | 2.0 | 5 | 1.0 | 2 | 0.4 | .. | ... | 17 |
| Onion | 4 | 0.8 | 2 | 0.4 | .. | ... | .. | ... | 6 |
| Orange | 7 | 1.4 | 5 | 1.0 | .. | ... | .. | ... | 12 |
| Orris root | 6 | 1.2 | 15 | 3.0 | 2 | 0.4 | .. | ... | 23 |
| Oyster | 7 | 1.4 | 5 | 1.0 | 1 | 0.2 | .. | ... | 13 |
| Parsnip | 1 | 0.2 | 3 | 0.6 | 1 | 0.2 | .. | ... | 5 |
| Pea | 8 | 1.6 | 10 | 2.0 | .. | ... | .. | ... | 18 |
| Peach | 2 | 0.4 | 5 | 1.0 | .. | ... | .. | ... | 7 |
| Pear | 9 | 1.8 | 5 | 1.0 | .. | ... | .. | ... | 14 |
| Pepper | 10 | 2.0 | 10 | 2.0 | 1 | 0.2 | .. | ... | 21 |
| Pineapple | 10 | 2.0 | 9 | 1.8 | .. | ... | .. | ... | 19 |
| Plum | 7 | 1.4 | 6 | 1.2 | .. | ... | .. | ... | 13 |
| Pork | 9 | 1.8 | 3 | 0.6 | .. | ... | .. | ... | 12 |
| Potato, white | 9 | 1.8 | 13 | 2.6 | 1 | 0.2 | .. | ... | 23 |
| Proteose | 3 | 0.6 | 11 | 2.2 | .. | ... | .. | ... | 14 |
| Prune | 10 | 2.0 | 8 | 1.6 | .. | ... | .. | ... | 18 |
| Rhubarb | 5 | 1.0 | 2 | 0.4 | .. | ... | .. | ... | 7 |
| Rice | 2 | 0.4 | 6 | 1.2 | .. | ... | .. | ... | 8 |
| Salmon | .. | ... | 3 | 0.6 | .. | ... | .. | ... | 3 |
| Spinach | 7 | 1.4 | 6 | 1.2 | .. | ... | .. | ... | 13 |
| Squash | .. | ... | 3 | 0.6 | 4 | 0.8 | .. | ... | 7 |
| Strawberry | 12 | 2.4 | 4 | 0.8 | .. | ... | .. | ... | 16 |
| Tea | 1 | 0.2 | 10 | 2.0 | .. | ... | .. | ... | 11 |
| Tobacco | 1 | 0.2 | 4 | 0.8 | .. | ... | .. | ... | 5 |
| Tomato | 6 | 1.2 | 6 | 1.2 | .. | ... | .. | ... | 12 |
| Turnip | 5 | 1.0 | 4 | 0.8 | 2 | 0.4 | .. | ... | 11 |
| Veal | 8 | 1.6 | 13 | 2.6 | 3 | 0.6 | .. | ... | 24 |
| Wheat, whole | 10 | 2.0 | 3 | 0.6 | .. | ... | .. | ... | 13 |

reactors, however, gave a previous history of protein hypersensibility, such as indigestion and hives, or of sensitiveness to egg, milk, strawberry and wheat, respectively. Nevertheless, in order to insure a reasonable margin of safety in the interpretation of results, all of these were included; the percentage of reactions in nonepileptic persons has been taken as 8 per cent, although this is perhaps unduly high for the reason just indicated.

It seems, therefore, that a group of epileptic patients is more likely to contain a higher percentage sensitive to protein than a similar aggregation of nonepileptic persons. The exact significance of this still remains to be determined. Furthermore, it must be remembered that, like other workers in this field, we have used raw protein extracts. Most proteins, however, are cooked before ingestion, and it is well known that the process of cooking brings about changes in these foodstuffs that

TABLE 4.—*Number of Positive Reactions in One Hundred Nonepileptic Controls*

| Protein | Plus Minus | One Plus | Two Plus | Three Plus | Comment |
|---|---|---|---|---|---|
| Barley | .. | 1 | 1 | .. | History of indigestion and hives in case of two plus reaction |
| Bean | 1 | .. | .. | .. | |
| Egg | .. | 1 | .. | .. | Rheumatic |
| Grape | 1 | .. | .. | .. | |
| Milk | 1 | .. | .. | .. | Rheumatic |
| Oat | .. | 1 | .. | .. | |
| Parsnip | 1 | .. | .. | .. | |
| Rhubarb | .. | 1 | .. | .. | |
| Strawberry | .. | .. | 1 | .. | Migraine |
| Wheat | 1 | .. | .. | .. | Migraine |

alter their character appreciably. Consequently, further study of the problem, including the use of cooked protein extracts, is warranted.

Up to the present time, we have not undertaken the treatment in these cases. In considering the subject of treatment in general, however, attention may be directed to certain comments appearing in our preliminary report which, it is thought, will bear reiteration at this point.

Broadly speaking, therapeutic efforts in protein-sensitive patients may be directed into two channels; namely, the elimination of the offending protein from the diet or the desensitization of the patient. Which method of procedure is to be preferred will depend largely on the particular circumstances in the individual case. Wallis and Nicol found that in some cases in which it was possible to adjust the diet on the basis of skin tests no further treatment was necessary. On the other hand, they also found it advantageous to attempt to desensitize a number of their patients by the judicious oral administration of peptone. Edgeworth [49] has likewise reported twenty cases in which he treated the

49. Edgeworth, F. H.: Intravenous Protein Therapy in Epilepsy, Brit. M. J. **2**:780 (Nov. 20) 1920.

patients by intravenous injections of a 5 per cent solution of peptone, beginning with a dose of 5 minims and gradually increasing it to 20 minims. Nine of these patients were at least temporarily benefited. Howell [50] considers that he is obtaining good results by restriction of diet together with the persistent use of a bacterial vaccine over a rather long period of time. In the experience of McCready and Ray, convulsions have returned with their usual intensity in a fasting patient soon after the return to a normal diet and to full activity.

In considering the efficacy of possible therapeutic measures, too much stress cannot be laid on the significance of recognizing the hypersensitive state in early childhood, as has already been emphasized by one of us (J. F. W.) and also by Howell. If an effort is made in every case of infantile convulsions to discover whether some offending protein is responsible for the seizures, it would seem that some cases of epilepsy might be prevented. When proteins enter the circulation, they attack the structures least able to resist their action. In cases of potential epilepsy, there may be the nerve centers, irritation of which causes convulsions. If such a situation is recognized before the continued action of the foreign protein has rendered the affected nerve centers intensely sensitive, and if prompt remedial measures are instituted, it should assist materially in reducing the later incidence of epilepsy.

## SUMMARY AND CONCLUSIONS

1. In a study of the occurrence of protein hypersensibility in 1,000 epileptic patients and in 100 nonepileptic controls, the incidence of protein sensitization in the Craig Colony group was found to be 37 per cent.

2. Protein sensitization was manifested in 56.8 per cent of the patients examined in the New Jersey State Village for Epileptics.

3. In the nonepileptic control group, 8 per cent showed positive reactions.

4. On the average, the percentage of patients hypersensitive to protein is higher in epileptic than in nonepileptic groups.

5. The significance of this ratio remains to be determined.

6. Raw protein extracts were employed in this study.

7. The problem of protein sensitization in epilepsy invites further investigation, in which the use of cooked protein extracts should be included.

8. In general, the treatment for this condition consists either in restriction of the diet or in desensitization.

9. The early recognition of the hypersensitive state is important from the standpoint of possible prophylaxis.

50. Personal communication to the authors.

# LEAD STUDIES

## XIV. EXPERIMENTAL STUDIES OF LEAD PALSY *

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The mechanism by which lead produces paralysis has not been studied thoroughly. Those investigations which have been reported have been almost entirely of a clinical and pathologic nature. Recent contributions to the chemistry and physiology of muscular contraction [1] and of the behavior of lead within the organism have suggested new methods for further study of the location and mechanism of the action of lead on nerve and muscle tissue, and the experiments described in this paper are the result of this newer knowledge.

### LITERATURE

Among the older investigators, Gusserow [2] was the first to obtain evidence suggestive of the direct action of lead on muscle. He reported that relatively large amounts of lead may be recovered from the muscles of rabbits with lead poisoning, but his observation was questioned by Heubel [3] and has never been confirmed. These experiments, however,

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1. Fletcher, W. M.: The Survival Respiration of Muscle, J. Physiol. **23**: 10, 1898-1899; The Relation of Oxygen to the Survival Metabolism of Muscle, ibid. **28**:474, 1902; The Influence of Oxygen on the Survival Respiration of Muscle, ibid. **28**:354, 1902; The Osmotic Properties of Muscle and the Modifications in Fatigue and Rigor, ibid. **30**:414, 1903-1904; Lactic Acid Formation, Survival Respiration and Rigor Mortis in Mammalian Muscle, ibid. **47**:361, 1913-1914. Fletcher, W. M., and Hopkins, F. G.: Lactic Acid in Amphibian Muscle, J. Physiol. **35**:247, 1906-1907. Hopkins, F. G.: The Chemical Dynamics of Muscle, Bull. Johns Hopkins Hosp. **32**:359 (Nov.) 1921. Hill, A. V.: The Mechanism of Muscular Contraction, Physiol. Rev. **2**:310, 1922. Meyerhoff, O.: Die Energiewandlungen im Muskel: I-VI. Arch. f. d. ges. Physiol. **182**:232 and 284, 1920; **185**:11, **188**:114, **191**:128, 1921; **195**:22, 1922. Embden, G., and Laquer, F.: Ueber die Chemie des Lactacidogens, Ztschr. f. physiol. Chem. **98**: 181, and **113**:1, 1916-1917. Embden, G., and Adler, E.: Ueber die physiologische Bedeutung des Weschsels des Permeabilitätszustandes von Muskelfasergrenzschichten, Ztschr. f. Physiol. Chem. **118**:1, 1922.

2. Gusserow, A.: Untersuchungen ueber Bleivergiftung, Arch. f. path. Anat. **21**:443, 1861.

3. Heubel, E.: Pathogenese und Symptome der chronischen Bleivergiftung, Berlin, A. Hirschwald, 1871.

drew attention to the possibility that lead might affect muscular activity. Muson [4] is reported to have immersed frogs in water containing lead and to have produced palsy of the hind limbs, as far as could be judged from voluntary effort and reflex response. Harnack [5] injected lead triethyl acetate into the dorsal sac of frogs and observed rapid exhaustion of muscular contractility and, in a short time, complete loss of excitability. He thought that muscle rather than nerve or nerve-ending was affected because direct stimulation of muscle evoked no stronger response than did stimulation through the nerve, and also because similar changes in muscular activity could be obtained with curarized frogs after injection of lead triethyl acetate. Since the toxicity of this compound depends not only on lead, but also on the triethyl group, these experiments cannot be taken as criteria of the action of lead on muscular tissue.

One of the phenomena observed by Harnack in the muscles that he considered poisoned with lead was delay in relaxation after stimulation. The same retardation of relaxation was seen by Cash,[6] who treated frogs with lead acetate. However, his work was entirely uncontrolled and most of his positive results were obtained at a warm temperature which in itself may affect the activity of muscles from cold-blooded animals. In well controlled experiments on frogs, Mellon [7] determined the effect of lead on fatigued muscle. To fatigue the gastrocnemius of one side, he stimulated it for several days and then injected lead acetate into the dosal sac. After excision, the previously fatigued muscle was able to perform much less work than that of the other side. All these investigators suggested that lead produces a definite physiologic lesion in muscle tissue.

Dozzi [8] raised the question whether lead might not affect isolated nerve as well as muscle. He used both nerve-muscle preparations (sciatic-gastrocnemius) from the same frog and immersed one nerve in physiologic sodium chloride solution and the other in isotonic lead acetate solution. In the nerve exposed to lead, the excitability, as judged by muscular response to minimal nerve stimulation, diminished markedly and finally disappeared completely. These experiments, however, can hardly be considered of much value because the lead solution was so

4. Muson, J. J.: Lead Poisoning in Frogs, New York M. J., July, 1877; quoted in Centralbl. f. d. med. Wissensch. **16**:480, 1878.

5. Harnack, E.: Ueber die Wirkungen des Bleis auf den tierischen Organismus, Arch. f. exper. Path. u. Pharm. **9**:152, 1878.

6. Cash, J. T.: The Contraction of Frog's Muscle After Administration of Lead, Arch. f. exper. Path. u. Pharm. **59**: (supp. vol.); **93**:106, 1908.

7. Mellon, R. R.: The Relation of Fatigue to Paralysis Localization in Plumbism, Arch. Int. Med. **12**:399 (Oct.) 1913.

8. Dozzi, L.: Studi sull'azione del piombo; azione del piombo sulla eccitabilita dei nervi motori, Sperimentali **66**:666, 1912.

concentrated (27 mg. of lead per cubic centimeter); the acidity, although not mentioned by Dozzi, must necessarily have been greater than is physiologic, and finally, the lead solution contained no balancing ions. This summary indicates that further knowledge of the action of lead on the function of the neuromuscular system is needed. Some of the investigations in this laboratory have suggested a means of studying the subject further. In experiments dealing with the effect of lead on red blood cells,[9] it was found that lead alters the surface of the corpuscle so that its permeability to water is changed. The question arises, therefore, as to whether lead may not act similarly on the surface of muscle and thus change its permeability. Various workers have studied the passage of substances through the surface of muscle in both directions under different conditions, and before describing our experiments it may be well to review briefly some of their results. Fletcher,[10] who studied the effect of fatigue and rigor on the intake of water by the isolated muscle of frogs, observed the development of marked variations of permeability from the normal. In his early work he also investigated the carbon dioxide output of muscle.

Experiments on the production and diffusion of lactic acid have been performed on isolated muscles by Fletcher, Hopkins,[11] Hill[12] and Meyerhoff.[13] In determinations of the diffusion of inorganic phosphates from muscle during rest and activity, Embden and his co-workers[14] have shown that inorganic phosphate is an intermediary product of glucose metabolism which diffuses in increased amounts during muscular activity. Since the quantity of inorganic phosphate in the muscle does not increase, the process of its formation is apparently reversible; Embden therefore concluded that the increased diffusion of inorganic phosphate is due to greater permeability of the cell membrane during activity and not to the production of more phosphate. Of the various methods of studying the changes in permeability of muscle, Embden's is the most satisfactory for our purpose, because of the ease of determining quantitatively the inorganic phosphate in solution; it has proved valuable in studying the effect of lead on the permeability of the surviving muscle of the frog.

## METHOD OF STUDY

The technic of the experiments carried out in this laboratory was as follows:

9. Aub, J. C.; Reznikoff, P., and Smith, D. E.: Lead Studies. III. The Effect of Lead on Red Blood Cells, J. Exper. Med. **40**:151, 173 and 189 (Aug.) 1924.

10. Fletcher (footnote 1, sixth reference).

11. Hopkins (footnote 1, seventh reference).

12. Hill (footnote 1, eighth reference).

13. Meyerhoff (footnote 1, ninth reference).

14. Embden et al. (footnote 1, tenth and eleventh references).

Both gastrocnemius muscles were removed from pithed frogs with as little injury as possible. They were handled only by the bone or tendon; they were treated in exactly the same way, and all manipulations were as nearly simultaneous as the procedure permitted. Each was placed in a beaker of known weight, containing 15 cc. of Ringer's solution,[15] and the weight of the muscle was determined. Both were kept in the solution through which oxygen was bubbled constantly to prevent rigor (Fletcher). After standing for one hour at room temperature, the muscles were raised above the fluid, carefully washed with Ringer's solution, and transferred to a second beaker containing fresh Ringer's solution. This procedure was repeated hourly until the phosphate content of the solution became low and practically constant. After this stage had been reached, in most cases within two or three hours after excision, one muscle was placed in Ringer's solution containing lead chloride (0.05 mg. of lead per cubic centimeter) and allowed to stand for one hour at 30 C.; the other was kept in the regular Ringer's solution under identical conditions. In a few experiments the muscle was exposed to lead before the lowest value was reached. The muscles were then washed and placed in fresh Ringer's solution hourly as before, at room temperature The Ringer's solution in each beaker was analyzed for inorganic phosphate, corresponding solutions from the control and "leaded" muscles being examined at the same time. In these determinations, a modification of the Bell-Doisy[16] method was used. No preliminary protein precipitation was necessary, and because the quantity of phosphate present was small the results were determined more accurately in Nessler tubes than in a colorimeter. The entire volume of fluid was compared with standards which were prepared for each test from stock "blood standard" phosphate solution. Relatively small differences in the phosphate content of these standards produced such marked differences of color that there was an error of only between 0.0005 and 0.0010 mg. of phosphate for each reading. The Ringer's solution containing lead was not analyzed, because the phosphate that diffused from the muscle combined with the lead as an insoluble lead phosphate and could not be determined by this method.

## RESULTS

Before the results of these experiments are presented in detail, it is necessary to point out that the tests were made at different times of the year, whenever animals could be obtained, and that therefore frogs of different species and of varying weights had to be used. Consequently, too much stress cannot be laid on an exact quantitative interpretation of the results. However, the figures show definitely that the diffusion of inorganic phosphate (mg. of phosphorus per gram of muscle per hour) increases markedly after "leading." Of thirty-five experiments, thirty-four demonstrated this clearly. Control muscles underwent no such

15. The Ringer's solution contained: sodium chloride, 0.6 per cent; potassium chloride, 0.03 per cent; calcium chloride, 0.02 per cent. No phosphate or carbonate was added because lead forms insoluble phosphate and carbonate. The $p_H$ was kept at 6.5, since lead hydroxide precipitates in more alkaline solutions.

16. Bell, R. D., and Doisy, E. A.: Rapid Colorimetric Methods for the Determination of Phosphorus in Urine and Blood, J. Biol. Chem. **44**:55 (Oct.) 1920.

change, except for a relatively slight increase in diffusion following stimulation in some experiments, but the diffusion curve followed the same course as that in Fletcher's carbon dioxide experiments, which was characterized by an immediate rapid decline succeeded by a gradual decrease in the rate of diffusion. Figures 1 and 2 show graphically the results of two striking experiments in which the increase in the diffusion of phosphate after exposure to lead is marked. The data from the

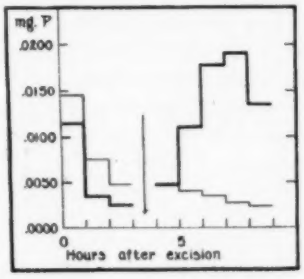


Fig. 1.—Effect of lead on the rate of diffusion of inorganic phosphates from muscle. The heavy line represents the rate from "leaded" muscle and the light line that from the control muscle. The arrow represents the period of exposure to lead (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution).

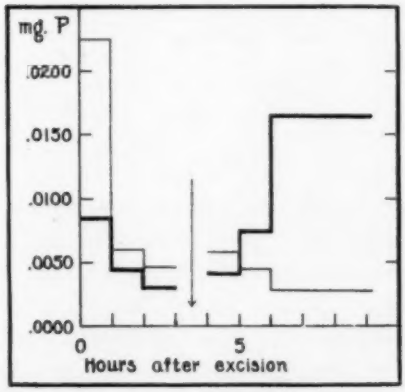


Fig. 2.—Effect of lead on the rate of diffusion of inorganic phosphates from muscle. The heavy line represents the rate from "leaded" muscle and the light line that from the control muscle. The arrow represents the period of exposure to lead (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution).

thirty-four positive experiments, collected in table 1, demonstrate variations in the degree of rise in phosphate diffusion; in the interval between the addition of lead and the appearance of the maximal increase; in the duration of the increase and in the return of the rate of phosphate diffusion to the minimum level.

TABLE 1.—*The Diffusion of Inorganic Phosphate from Normal and "Leaded" Muscle* *

| Number of Experiment | Content of Ringer's Solution in Mg. of Phosphorus per Gm. of Muscle per Hour: Minimum Diffusion from "Leaded" Muscle | Maximum Diffusion from: Corresponding Value of Control Muscle | Maximum Diffusion from: "Leaded" Muscle after Exposure to Lead | Corresponding Value of Control Muscle | Per Cent Variation in Phosphate Diffusion: "Leaded" Muscle | Control Muscle in Corresponding Time | Duration of Increased Diffusion from "Leaded" Muscle: Before Return to Normal, Hours | Without Return to Normal, Hours | Development of Maximum Diffusion after "Leading," Hours | Duration of Maximum Diffusion, Hours |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.002 | 0.010 | 0.011 | 0.011 | +450 | +10 | ... | 4 | 4 | 1 |
| 2 | 0.008 | 0.012 | 0.026 | 0.008 | +770 | —30 | ... | 4 | 3 | 2 |
| 3 | 0.005 | 0.006 | 0.017 | 0.006 | +240 | 0 | ... | 4 | 2 | 2 |
| 4 | 0.003 | 0.013 | 0.015 | 0.008 | +400 | —40 | ... | 4 | 3 | 1 |
| 5 | 0.003 | 0.004 | 0.011 | 0.006 | +270 | +50 | ... | 4 | 3 | 1 |
| 6 | 0.004 | 0.007 | 0.010 | 0.005 | +150 | —30 | ... | 4 | 2 | 1 |
| 7 | 0.003 | 0.005 | 0.015 | 0.004 | +400 | —20 | ... | 5 | 2 | 3 |
| 8 | 0.003 | 0.004 | 0.007 | 0.004 | +130 | 0 | ... | 5 | 3 | 2 |
| 9 | 0.002 | 0.003 | 0.008 | 0.003 | +300 | 0 | ... | 5 | 3 | 2 |
| 10 | 0.004 | 0.006 | 0.014 | 0.006 | +250 | 0 | ... | 5 | 2 | 1 |
| 11 | 0.005 | 0.006 | 0.017 | 0.004 | +240 | —30 | 9 | .. | 3 | 1 |
| 12 | 0.005 | 0.007 | 0.011 | 0.008 | +120 | +10 | 7 | .. | 3 | 1 |
| 13 | 0.007 | 0.009 | 0.015 | 0.009 | +110 | 0 | ... | 7 | 6½ | 1 |
| 14 | 0.008 | 0.004 | 0.018 | 0.005 | +130 | +30 | ... | 7 | 6½ | 1 |
| 15 | 0.008 | 0.008 | 0.010 | 0.004 | + 30 | —50 | 4 | .. | 3 | 1 |
| 16† | 0.003 | 0.005 | 0.016 | 0.003 | +430 | —40 | ... | 5 | 3 | 3 |
| 17 | 0.002 | 0.005 | 0.019 | 0.003 | +850 | —40 | ... | 5 | 4 | 1 |
| 18‡ | 0.001 | 0.002 | 0.008 | 0.002 | +700 | 0 | ... | 4 | 4½ | .. |
| 19§ | 0.006 | 0.007 | 0.023 | 0.005 | +280 | —30 | ... | 4 | 2½ | 2 |
| 20# | 0.003 | 0.004 | 0.020 | 0.003 | +570 | —30 | ... | 8 | 4 | 2 |
| 21‡ | 0.004 | 0.006 | 0.008 | 0.004 | +200 | —30 | ... | 8 | 8 | .. |
| 22# | 0.005 | 0.006 | 0.016 | 0.005 | +250 | —20 | ... | 8 | 7 | 1 |
| 23§ | 0.002 | 0.003 | 0.008 | 0.003 | +300 | 0 | ... | 7 | 4½ | 4½ |
| 24‡ | 0.003 | 0.003 | 0.011 | 0.003 | +270 | 0 | ... | 6½ | 7 | .. |
| 25‡ | 0.001 | 0.001 | 0.013 | 0.002 | +1200 | +100 | ... | 6½ | 6½ | .. |
| 26# | 0.011 | 0.009 | 0.024 | 0.013 | +120 | +40 | ... | 6¼ | 3 | 1 |
| 27# | 0.006 | 0.005 | 0.020 | 0.003 | +230 | —40 | 7½ | .. | 2 | 1 |
| 28# | 0.008 | 0.005 | 0.012 | 0.002 | + 50 | —60 | ... | 9½ | 7½ | 1 |
| 29‡ | 0.005 | 0.003 | 0.007 | 0.003 | + 40 | 0 | ... | 8¼ | 7¼ | .. |
| 30‡ | 0.006 | 0.009 | 0.019 | 0.012 | +220 | +30 | ... | 5¼ | 2 | 1 |
| 31‡ | 0.002 | 0.005 | 0.023 | 0.004 | +1050 | —20 | ... | 6 | 5½ | 1 |
| 32‡ | 0.008 | 0.008 | 0.022 | 0.009 | +180 | +10 | ... | 4 | 4 | .. |
| 33‡ | 0.010 | 0.016 | 0.024 | 0.011 | +140 | —30 | ... | 3 | 2 | 1 |
| 34‡ | 0.013 | 0.016 | 0.027 | 0.014 | +110 | —10 | ... | 4 | 4 | .. |

* Average increase of phosphate diffusion from "leaded" muscle, +320 per cent. Average decrease of phosphate diffusion from control muscle in corresponding period, —10 per cent.
† Still maximal at last determination.
‡ Muscles stimulated. Experiment stopped while diffusion was maximal.
§ Muscles stimulated. Still maximal at last determination.
# Muscles stimulated.

TABLE 2.—*Increase of Diffusion of Inorganic Phosphate from "Leaded" Muscle* *

| Per Cent Increase after "Leading" | Number of Experiments |
|---|---|
| Less than 100 | 3 |
| Between 100 and 200 | 9 |
| Between 200 and 300 | 10 |
| Between 300 and 400 | 2 |
| Between 400 and 500 | 4 |
| Between 500 and 600 | 1 |
| Between 600 and 700 | 0 |
| Between 700 and 800 | 2 |
| Between 800 and 900 | 1 |
| More than 1,000 | 2 |

* Average change of phosphate diffusion from "leaded" muscle, +320 per cent. Average change of phosphate diffusion from control muscle, —10 per cent.

A summary of these results (table 2) shows that the average rate of diffusion increased, after exposure to lead, 320 per cent above the lowest value. In only three cases was this increase less than 100 per cent. In nine experiments it was between 100 and 200 per cent of the minimum, in ten between 200 and 300 per cent, and in two more than 1,000 per cent. During the same period the average rate of phosphate diffusion from the control muscles decreased 10 per cent. In the composite curve of all the experiments (fig. 3), the marked difference in phosphate diffusion between the "leaded" and control muscles is clear. It should be pointed out that in some of the experiments (ten) the low value, before the beginning of the rise caused by lead, occurred late and that therefore the composite chart, showing the average diffusion for each hour, does not give as good an indication of the degree of change as can be obtained from the study of the individual experiments in table 1. The length of time elapsing after the removal of the muscles from the lead solution before the diffusion of phosphate became maximal

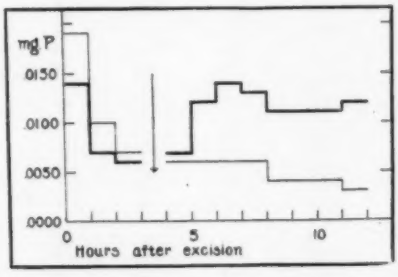


Fig. 3.—Composite chart showing effect of lead on the rate of diffusion of inorganic phosphates from muscle. The heavy line represents the rate from the muscle exposed to lead solution and the light line that from the control. The arrow represents the period of exposure to lead (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution).

varied from two (seven experiments) to eight hours (one experiment). In the majority of cases (ten experiments), the peak was reached within three hours. Of the twenty-seven experiments which were continued after the peak was reached, eighteen showed a sustained maximal diffusion for only one hour, and six for two hours. In the other three, the diffusion remained maximal until the experiment was terminated—three hours in two cases, and four and one-half hours in one case. In only four experiments did the rate of diffusion return to the low control value during the course of the observations. In one case the curve did not return to its original low level even nine and one-half hours after exposure to lead.

Factors other than exposure to lead may alter the rate of phosphate diffusion. Injury increases the permeability of muscle to inorganic phosphate; but in this series of experiments the results obtained in the

controls indicated that this was negligible. That stimulation increases the rate of diffusion was shown by Embden; but the degree of increase is never of the same magnitude as that caused by lead. In twenty-nine experiments with normal muscles, stimulation increased the diffusion so little that the figures usually fell well within the limits of experimental error. Increases of between 0.001 and 0.002 mg. of phosphorus per gram of muscle per hour followed only eight of 100 stimulations; and only once did the output increase as much as from 0.008 to 0.016 mg. In this case, stimulation was so frequent that rigor probably resulted. In most of our experiments, rigor, which of course increases the rate of diffusion of phosphate markedly, was avoided by providing a constant supply of oxygen and by preventing undue fatigue. Although the relationship between rigor and the muscular changes caused by lead cannot be considered in detail here, it will be of interest to remember that rigor is supposed to be due to the acid products of fatigue. Examination of muscles after exposure to lead demonstrates that they are shrunken, of rubbery consistency and lusterless—in fact, comparable in appearance to muscles in rigor.

Other observations merit consideration. If a "leaded" muscle is treated with ammonium sulphide and examined under the microscope, all the lead appears on the surface and none can be demonstrated deep in the muscle. Another fact is also of interest in this connection. When a muscle is exposed to lead, there is a change in the reaction of the surrounding solution, in one case from $p_H$ 6.5 to 4.8; in a second experiment to $p_H$ 5.5, and in a third to $p_H$ 6.1. Such an increase in acidity agrees with the results of our work on the effect of lead on red blood cells, which show that soluble lead salts unite with the inorganic phosphate to form insoluble lead phosphate with the liberation of free acid. To determine the effect of acid on the permeability to inorganic phosphate, acid Ringer's solution was added to muscles. In one case in which the $p_H$ of the Ringer's solution was 4.5, the permeability of the treated muscle remained practically like that of the control, but in two experiments in which the $p_H$ of the Ringer's solution was 3.5, the rate of phosphate diffusion increased markedly at once. The maximum increase was brief, but throughout the experiment the rate of diffusion remained constant and did not decrease as did that of the control. In one case it remained twice as high as the original rate before exposure to acid. The maximum increase in diffusion due to acid was 140 per cent in one of those experiments, and in the other 520 per cent. This type of experiment, however, is not comparable to those in which the muscle is exposed to a lead salt, for in the latter acid is produced in the tissue of the muscle and the buffer phosphates must be diminished by their interaction with lead. These acid experiments offer further evidence that when lead salts act on isolated muscle the reaction that probably occurs is similar to that demonstrated with red blood cells.

Such a striking change in the permeability of the surface of muscle to inorganic phosphate suggests that lead may have a demonstrable effect on the activity of isolated muscles. To determine this, experiments were performed in which nerve-muscle preparations (sciatic-gastrocnemius) were removed from pithed frogs and placed in Ringer's solution in specially constructed chambers. One muscle was exposed to lead (0.05 mg. of lead per cubic centimeter) and the other was kept in Ringer's solution as a control. They were stimulated both directly and through their nerves, and the rate of onset of fatigue and the degree of recovery were noted. The apparatus illustrated in figure 4 was devised for these procedures.

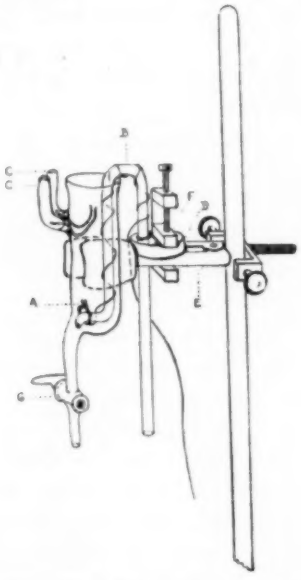

Fig. 4.—Nerve-muscle stimulation and diffusion chamber.

The muscle is attached by the Achilles tendon to the platinum hook *A*, which is fastened to the bottom of the oxygen inlet tube *B*. The chamber itself, made of glass, is 8 cm. high and 2.5 cm. wide. About 2.5 cm. from the top two glass tubes, *C*, *C* (4 mm. in diameter) are sealed into the wall of the chamber. Through these, platinum wires run into the chamber so that when the tubes are filled with mercury they may serve as stimulating electrodes for the nerve. The oxygen inlet tube runs through the cork *D* which is held firmly against the chamber *E* by means of a heavy screw clamp *F*. Wound about the platinum hook *A* and the oxygen inlet tube is a fine insulated wire which permits the hook to serve as one of the muscle stimulating electrodes. The other muscle electrode consists of a platinum S-shaped hook run through the knee joint and attached to one end of a fine copper wire which has been made soft by heat. The other end of this wire is fastened to an ordinary muscle lever for recording muscular contractions. At the bottom of the muscle chamber a stopcock *G* is inserted, through which Ringer's solution may be admitted and removed by gravity pressure. With such an apparatus, the muscle may be con-

tinually bathed in Ringer's solution which can be changed at regular intervals and through which oxygen may be bubbled constantly, so that both the rate of phosphate diffusion and the character of muscular contractions can be readily determined.

In each experiment two such chambers were used, one for the control and the other for the "leaded" muscle. The electrodes were connected in series so that both nerves or both muscles were stimulated simultaneously by the same current. This permitted direct and controlled comparison of the two muscles, and made unnecessary an exact regulation of the stimulating current in the different experiments. The recording levers (the ordinary straw variety) were of equal length; they were always afterloaded, and were usually weighted with from 5 to 10 Gm. In any given experiment the same weight was applied to both levers at the same distance from the fulcrum. The stimulating electrodes were attached to the secondary post of a standard student's induction coil. A metronome made and broke the primary current at regular intervals. In the secondary circuit a rocking key, which permitted the current to be switched to either nerve or muscle, was inserted. In almost all experiments the stimuli were maximal, and in every case control records were made before lead was added. Usually nerve and muscle were stimulated alternately.

Thirteen experiments were performed with tetanic stimulation. In eight cases the control muscle remained in good condition, although the "leaded" muscle became fatigued rapidly. In most experiments it did not regain its normal condition. Figure 5 illustrates one experiment in which the muscle was stimulated directly and the rate of phosphate diffusion was determined hourly (fig. 6). A description of the experiment follows:

a. m.
8:58 In first Ringer's solution
9:48 Nerve stimulated, 1
9:50 Muscle stimulated, 2
9:58 In second Ringer's solution, 20.3 C.
11:02 Upper muscle in Ringer's solution, lower in lead solution, 31.5 C.
p. m.
12:08 In third Ringer's solution, 20.9 C.
12:12 Muscle stimulated, 3
12:18 Muscle stimulated, 4
12:24 Muscle stimulated, 5
12:38 In fourth Ringer's solution, 20.8 C.
12:48 Muscle stimulated, 6
1:38 In fifth Ringer's solution, 20.9 C.
2:03 Muscle stimulated, 7
2:19 Muscle stimulated, 8
2:38 In sixth Ringer's solution
3:02 Muscle stimulated, 9
3:25 Muscle stimulated, 10
3:31 Muscle stimulated, 11
3:38 Removed to sixth Ringer's solution, 20.7 C.

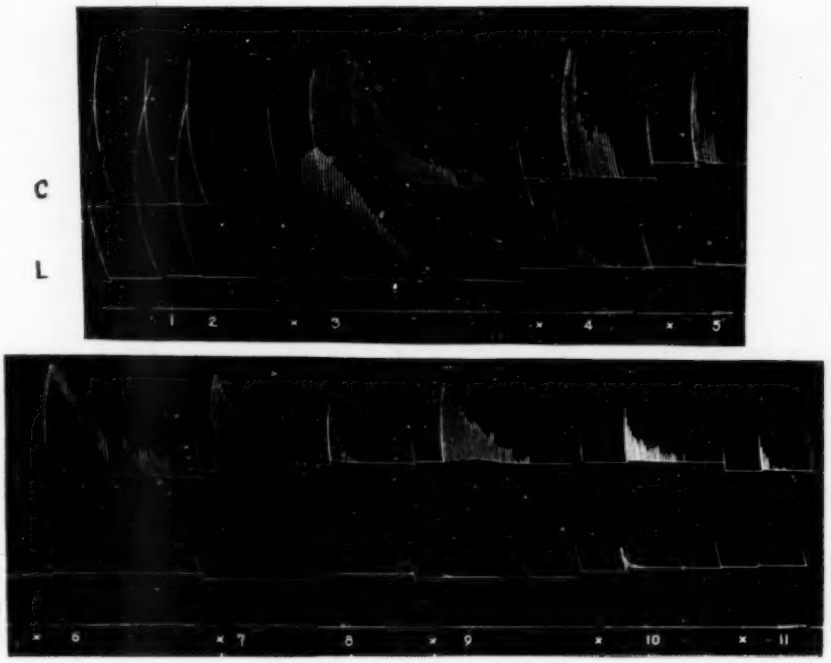


Fig. 5.—Muscular response to intermittent tetanic stimulation before and after "leading": *C*, tracing made by the control muscle; *L*, tracing made by the "leaded" muscle (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution). The figures indicate the periods of stimulation; the crosses represent readjustment of the after-loading of the muscles.

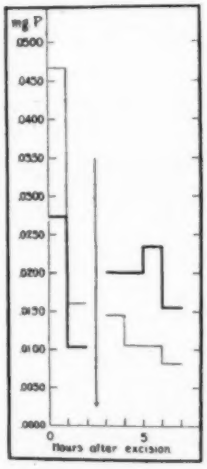


Fig. 6.—Variations of the rate of inorganic phosphate diffusion from normal and "leaded" muscles during tetanic stimulation. The heavy line represents the rate from the "leaded" muscle (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution) and the light line that from the control muscle.

This experiment demonstrates several interesting facts. The "leaded" muscle became fatigued much more rapidly than the control (3 and 4) and failed to recover (5). Apparently lead alone cannot cause immediate injury to the muscle, for the "leaded" muscle gave excellent initial contractions after removal of the lead-Ringer's solution (3), but fatigue followed a series of such contractions rapidly. This occurred in all experiments and demonstrates that the action of lead on

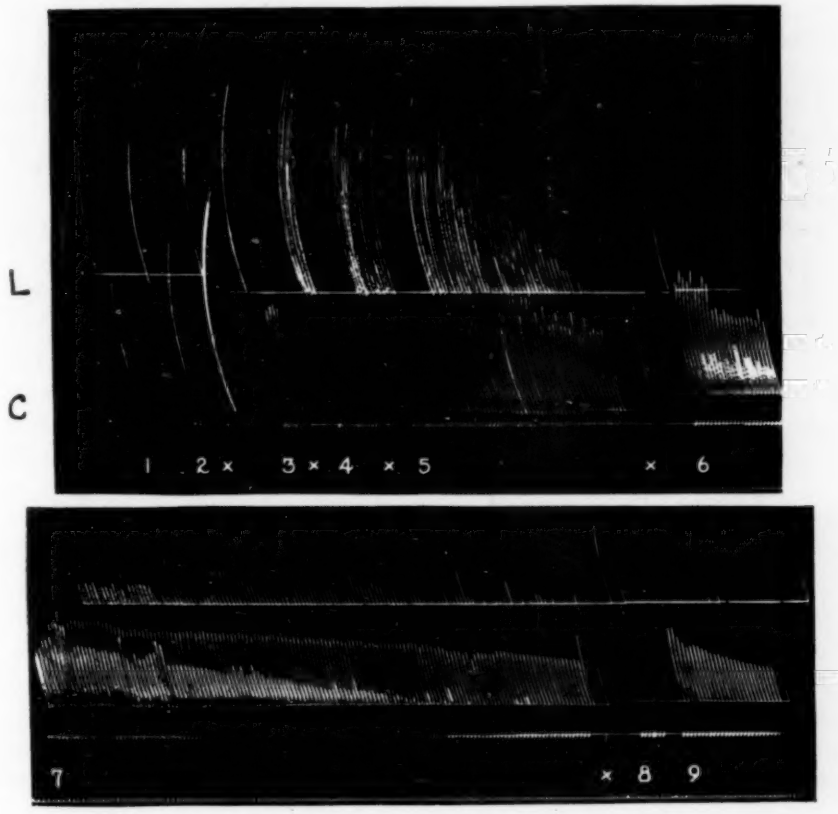


Fig. 7.—Muscular response to make and break stimulation: *L*, the tracing made by the "leaded" muscle (0.05 mg. of lead as lead chloride per cubic centimeter of Ringer's solution); *C*, that of the control.

muscle is manifested only after muscular activity occurs. Comparison of the diffusion curve and the muscle tracing shows that the greatest quantity of phosphate diffuses during the first, second and especially the third hour after exposure to lead (third, fourth and fifth Ringer's solution) when the muscle is most fatigued. The slight return of contraction evident at 9, 10 and 11 occurs simultaneously with a decrease in the rate of diffusion.

In five of the thirteen experiments, no difference in the rate of onset of fatigue in the control and "leaded" muscles could be seen. In these cases the muscles performed an excessive amount of work, and rapid fatigue ensued. In none of these tests, however, did the control muscle fatigue more rapidly than the "leaded" muscle.

Since control muscles seemed to be fatigued so readily with tetanic stimulation, a series of experiments (ten) was performed with make and break stimulation. The results showed definitely that after an initial period of sustained uniform contraction, the "leaded" muscle became fatigued much more rapidly and completely, and recovered with much greater difficulty than the control in every case. Figure 7 illustrates one of these experiments, in which the levers were weighted with only 2.5 Gm., so that an excessive amount of work was not performed. These investigations, therefore, indicate that lead interferes markedly with the function of isolated muscle. Stimulation produces fatigue much more rapidly after exposure to lead, while recovery, slight at best, in most cases does not occur at all.

### EFFECT OF LEAD ON NERVE

Because of the clinical designation of lead palsy as a peripheral neuritis as well as of the occurrence of pathologic lesions in peripheral nerves, the impression is prevalent that lead acts specifically on peripheral nerve. The only experimental study of this problem reported in the literature was made by Dozzi and has already been shown to be of little value. The action of lead on isolated nerve has been investigated in this laboratory by means of the Adrian[17] narcosis chamber. In these experiments the standard procedure was to excise the two nerve-muscle preparations of a frog, place the sciatic nerve of each in a narcosis chamber, and between the point of stimulation and the muscle to treat one with normal Ringer's solution as a control and the other with a Ringer's solution, of the same hydrogen ion concentration, which contained lead chloride. The muscles were placed in moist chambers, and the nerves were stimulated by the electrodes of the two narcosis chambers connected in series. In four experiments the conductivity, as judged by muscular response, was exactly the same in both nerves. In one of these the strength of lead used was 0.05 mg. of lead (as lead chloride) per cubic centimeter of Ringer's solution; in two, the concentration was 0.1 mg., and in the fourth the nerve was treated with 0.23 mg. of lead per cubic centimeter of Ringer's solution for one hour, and then for another hour with Ringer's solution containing 0.46 mg. per cubic centimeter, the largest quantity soluble in Ringer's solution of $p_H$ 6.5. In none of these experiments could any difference between

17. Adrian, E. D., and Lucas, K.: On the Summation of Propagated Disturbances in Nerve and Muscle, J. Physiol. **44**:68, 1912.

the conductivity of the "leaded" and control nerves be detected. At the end of the test, the nerves were always placed in a solution of ammonium sulphide to determine whether there had actually been a deposition of lead; the invariable black discoloration of the "leaded" nerves indicated that this had occurred. As far as can be judged from this work, therefore, lead produces no decrement in nerve conduction.

To check these results an attempt was made to determine the action currents of both nerve and muscle as a delicate index of function by the string galvanometer, lent by Dr. Alexander Forbes and Miss Anne Hopkins, who assisted us in these experiments. In one of a pair of nerve-muscle preparations the nerve, and in the other the muscle, was exposed to lead. Because a great number of stimulating and leading-off electrodes must be placed in a small space for such work, there was great difficulty in avoiding artefacts. Further complications were introduced by the necessity of performing all manipulations simultaneously on both "leaded" and control structures. In one test a distinct action current was seen in the "leaded" nerve, but not in the "leaded" muscle. This experiment was, however, unsatisfactory because both muscles were not fatigued at the same time. Another experiment in which this defect was avoided demonstrated distinctly that after fatigue the action current of the "leaded" muscle diminished rapidly and soon disappeared entirely, while that of the control muscle returned to normal within a short while and persisted until the end of the experiment. Similar, undiminished action currents were obtained from both normal and "leaded" nerves. Thus, the distinct inhibitory action of lead on isolated muscle and the lack of deleterious action on isolated nerve are confirmed.

### PALSY IN VIVO

In the explanation of lead palsy, as it occurs in life, the experiments already described serve merely as preliminary and suggestive observations which must be correlated with the production of palsy in living animals if they are to have any important practical significance. The ample evidence that, in life, lead paralysis develops in muscles that are fatigued [18] links the problem of lead palsy with the chemistry of muscular fatigue and suggests a method of investigation in intact animals.

18. Meyer, M.: Die Elektrizität in ihrer Anwendung auf praktische Medizin, Berlin, 1854, quoted by Weill. Moebius: Ueber einige ungewöhnliche Fälle von Bleilähmung, Centralbl. f. Nervenheilk. **1**:6, 1886; quoted by Stieglitz: Eine experimentelle Untersuchung ueber Bleivergiftung mit besondere Berücksichtigung der Veränderungen am Nervensystem, Arch. f. Psychiat. **24**:49, 1892. Weill, G.: Zur Frage von der Lokalization der Bleilähmung, Inaug. Diss., Strassburg, 1892. Edinger, L.: Der Anteil der Funktion an der Entstehung von Nervenkrankheiten, Wiesbaden, Bergmann, 1908, p. 67. Teleky, L.: Zur Kasuistik der Bleilähmung, Deutsche Ztschr. f. Nervenh. **37**:234, 1909. Oliver, T.: Lead Poisoning, London, H. K. Lewis, 1914, p. 148.

Attempts were made to produce palsy in the frog. Lead was injected frequently into the dorsal sac, and one leg was fatigued by intermittent stimulation over the sciatic nerve for several days. In most of the experiments there were no differences between fatigued and control muscles and when any difference could be found there was always a question of injury to tissue. There are two objections to this method: first, lead salts administered subcutaneously are precipitated at the site of injection and are therefore only slightly and slowly absorbed; second, the mere response to electrical stimulation probably results in neuromuscular junction fatigue without necessarily causing fatigue in the muscle comparable to that obtained by lifting weights.

Consequently, an attempt was made to produce palsy in mammals by fatiguing the extensor muscles of one limb by voluntary contraction. At first rabbits were used, but they did not prove as satisfactory as cats which later were used exclusively. A lead carbonate suspension was injected into the lungs of some animals through the trachea, and others were kept as controls. In order to produce unilateral fatigue, weights varying from 70 to 100 Gm. were attached with adhesive plaster to the dorsal surface of the right forepaw of all animals. These rested on cotton pads, and since they apparently did not disturb the animals they were removed only to allow occasional inspection of the limb. The animals were exercised daily in a revolving drum (lent by Dr. M. J. Rosenau) to produce a marked degree of fatigue in the extensor muscles of the right forepaw by constant raising of the weights. When a distinct difference between the weighted limb and the other became apparent, the animals were allowed to rest for twenty-four hours with the weights removed. Then, under urethane anesthesia, the musculospiral nerves (radial) and the extensor muscles were exposed and submitted to various physiologic tests. The threshold of these muscles to nerve stimulation, and in some experiments to direct stimulation, was determined. Attempts also were made in some cases to obtain action currents, and to demonstrate differences between the degree of fatigue in the weighted and unweighted muscles following stimulation, but because of difficulties inherent to the experiments, these usually proved unsuccessful. In all experiments the electrodes were connected in series, so that both sides were stimulated equally and simultaneously.

Before the experimental results are considered in detail, a brief description of the typical behavior of the animals may be of interest. After the administration of lead, all the cats lost weight rapidly, and within one or two weeks showed distinct lead lines and became easily fatigued by exercise. The weighted foot showed distinct signs of weakness after about two weeks of exercise. This was manifested by difficulty in extending the foot when the weight had been removed for twenty-four hours, and was especially marked if the animal was held

by its neck and permitted to reach for the top of a window ledge. Some of the animals limped decidedly in walking. When the weights were still attached, the contrast between the "leaded" and control animals was even more striking. Those suffering from plumbism could not lift the weighted paw without great effort and then only with the aid of the upper leg muscles, while the control animals lifted both paws with equal ease. After the animals had been run in the drum, these differences were accentuated. The "leaded" cats tired much more quickly and to a greater degree than did the normal animals and exhibited a striking fatigue of the weighted limb, which usually completely prevented extension of the paw. They took shorter steps with the weighted limb while

TABLE 3.—*Threshold Determinations in Rabbit 489*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil | |
|---|---|---|---|---|
| | | | Left Side, Cm. | Right (Weighted) Side, Cm. |
| Nerve | 2 | Break | 10 | 8.25† |
| Nerve | 3 | Break | 13 | 8.5 |
| Muscle | 3 | Break | 13 | 8.5 |
| Muscle* | 3 | Break | 11 | 7.75 |
| Muscle | 3 | Break | 12.25 | 8.0 |

* Poles of secondary reversed.
† The lower the figure, the greater the current.

TABLE 4.—*Threshold Determinations in Rabbit 493*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil | |
|---|---|---|---|---|
| | | | Left Side, Cm. | Right (Weighted) Side, Cm. |
| Nerve | 3 | Break | 13 | 13 |
| Muscle | 3 | Break | 8.75 | 9.25 |

running and seemed to lean toward the left. This description fits nearly all of the animals, and individual variations will be mentioned in the protocols. The threshold experiments were performed on one "leaded" rabbit and its control and on four "leaded" and two control cats. Of the "leaded" cats, one showed little limitation of extension in the weighted paw before the experiment. One died in convulsions and three of inanition before differences between the weighted and unweighted limbs seemed sufficiently marked to warrant a determination of their thresholds. Two animals died during the operation.

## PROTOCOLS

### EXPERIMENT 1.

*Rabbit 489, "Leaded."*—Lead carbonate was injected intratracheally three times. Two hundred milligrams of lead, as lead acetate, was given by the stomach tube five times. The weight attached to the right forepaw was

60 Gm. The animal was run in the drum for fifty-two days (7.3 miles). Marked stippling of red blood cells was present during this period.

The nerve was too short to permit the recording of action currents. No fatigue record was obtained, as the animal was in too poor condition.

*Rabbit 493, Control.*—This animal was treated in every way like 489 except that it received no lead.

The most striking feature of this experiment is the similarity between the threshold of the unweighted muscle of the "leaded" animal and that of both unweighted and weighted muscles of the control, when stimulated by nerve with uniform current. In the "leaded" rabbit, the threshold of the weighted muscle to stimulation through the nerve was much higher. There is the same relative difference between thresholds when stimulation is applied directly to the muscle. In the control, the slight difference between the two sides probably falls within the limits of normal variation. The difficulty of applying the muscle electrodes,

TABLE 5.—*Threshold of Radial Nerves and Brachioradialis Longus Muscles in Cat 480*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil | | |
|---|---|---|---|---|---|
| | | | Left Side | | Right (Weighted) Side, Cm. |
| | | | Cm. | Rotation | |
| Nerve | 4 | Break | 13 | 85 degrees | 9.5 |
| Muscle | 4 | Break | 12.5 | | 9.0 |

however, to exactly corresponding points of the muscles detracts from the value of the results obtained from muscle stimulation.

EXPERIMENT 2.

*Cat 480, "Leaded."*—Lead carbonate was injected intratracheally once. A 60 Gm. weight was attached to the right forepaw. The animal was run in the drum for fifteen days (2.3 miles). The body weight fell from 2.7 to 2.2 Kg. After an interval of seven days the animal was again exercised for eight days (0.42 miles). The body weight was from 2.2 to 2.3 Kg. The weight was changed to 100 Gm. and the animal was run for two days (0.18 miles). The weight was again changed to 60 Gm., and the animal was run for five days (0.44 miles). The body weight was 2.5 Kg. One hundred and fifty milligrams of lead was given by stomach tube twice. With a weight of 80 Gm. attached, the animal was run for five days (0.73 miles). The body weight was 2.7 Kg. The total length of the run was thirty-five days (4 miles).

As the animal became unconscious under urethane anesthesia, the right forepaw was held completely flexed.

An attempt to record action currents from the nerve and muscle of each limb proved unsuccessful because of artefacts; this spoiled the preparation for fatigue tests.

*Cat 492, Control.*—This animal was treated in every way like 480 except that no lead was administered. Under anesthesia both forepaws were equally active and were held in the same position.

Since the threshold for stimulation through the nerve was the same on both sides, stimulation was not applied directly to muscle.

In this experiment the difference between the right (weighted) and left paws after exposure to lead is similar to that in the experiment with the rabbits. The threshold of the left, unweighted muscle is apparently normal, similar to those of the control, even after exposure to lead.

EXPERIMENT 3.

*Cat 115, "Leaded."*—Lead was given intratracheally once. The weight placed on the right forepaw was 70 Gm. The animal was exercised in the drum for a

TABLE 6.—*Threshold of Radial Nerves and Brachioradialis Longus Muscles in Cat 492*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil | | | |
|---|---|---|---|---|---|---|
| | | | Left Side | | Right (Weighted) Side | |
| | | | Cm. | Rotation | Cm. | Rotation |
| Nerve | 4 | Break | 13 | 80-85 degrees | 13 | 80-85 degrees |

TABLE 7.—*Threshold Determinations in Cat 115*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil | | | |
|---|---|---|---|---|---|---|
| | | | Left Side | | Right (Weighted) Side | |
| | | | Cm. | Rotation | Cm. | Rotation |
| Nerve | 4 | Break | 13 | 85 degrees | 12.5 | |
| Nerve | 4 | Break | 13 | 85 degrees | 13 | 30 degrees |
| Nerve | 4 | Make and break | 13 | 85 degrees | 9.5 | |
| Nerve | 4 | Make and break | 13 | 45 degrees | 10.75 | |
| Muscle | 4 | Break | 11 | | 7.5 | |
| Muscle | 4 | Make and break | 7.5 | | 5.5 | |
| Muscle | 4 | Make and break | 7.5 | | 5.5 | |
| Muscle | 4 | Make and break | 7.5 | | 5 | |

period of forty-two days, during which it rested for an interval of fourteen days (ran 3.3 miles). Body weight during this time fell from 2.8 to 2.5 Kg. and then gradually rose to 3.1.

Records of action currents could not be taken because the string galvanometer was out of order.

In making the fatigue curves the levers were loaded with 30 Gm., and the stimuli (break shocks) were maximal. No difference in the rate of fatigue of the right and left sides could be demonstrated. Neither side was completely fatigued.

Although the difference between the weighted and unweighted muscles is not as striking as in the previous experiments, it is distinct and constant. As this animal had been exercised for only twenty days, the muscles were probably little fatigued. The failure to demonstrate a

difference in the fatigue curves of the two sides may be due to insufficient weight on the muscles.

EXPERIMENT 4.

*Cat 107, "Leaded."*—Lead was injected intratracheally once. The animal was run in the drum for seventeen days (2.6 miles). One hundred and fifty milligrams of lead was then given by stomach tube on four successive days and a weight of 70 Gm. was attached to the right forepaw. The animal was then run again for fourteen days (2.7 miles). After the first administration of lead, the body weight of the animal fell from 2.5 to 2 Kg. Just before the second administration the weight had risen to 2.3 Kg., but it again fell to 1.9 after the last day of exercise. The animal was weak and in a poor condition.

TABLE 8.—*Threshold Determinations in Cat 107*

| Stimulation of | Time of Stimulation | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil: Left Side Cm. | Left Side Rotation | Right (Weighted) Side Cm. | Right (Weighted) Side Rotation |
|---|---|---|---|---|---|---|---|
| Nerve | 2:50 p.m. | 2 | Break | 13 | 75 degrees | 13 | 45 degrees |
| Nerve | 3:00 | 2 | Make and break | 13 | 45 degrees | 13 | 5 degrees |
| Nerve | 3:05 | 2 | Break | 13 | 75 degrees | 13 | 20 degrees |
| Nerve | 4:15 | 2 | Break | 13 | 85 degrees | 13 | 25 degrees |
| Nerve | 4:17 | 2 | Make and break | 13 | | 11 | |
| Nerve | 4:45 | 2 | Break | 13 | 45 degrees | 12.25 | |
| Nerve | 5:35 | 2 | Break | 12.25 | | 12.25 | |
| Nerve | 6:45 | 2 | Break | 11 | | 11 | |
| Nerve | 7:45 | 4 | Break | 11 | | 10 | |
| Nerve | 8:17 | 4 | Break | 9 | | 5.25 | |

TABLE 9.—*Threshold Determinations in Cat 119*

| Stimulation of | Voltage of Primary Current | Stimulation with | Threshold Stimulus Position of Secondary Coil: Left Side Cm. | Left Side Rotation | Right (Weighted) Side Cm. | Right (Weighted) Side Rotation |
|---|---|---|---|---|---|---|
| Nerve | 2 | Break | 13 | 75 degrees | 13 | 75 degrees |

While walking and while becoming narcotized with urethane, it showed signs of distinct extensor weakness in the right forepaw.

Because the electrodes could not be placed on corresponding parts of the muscles, direct muscle stimulation proved unsatisfactory. The animal was in too poor condition to give good action currents. Constant stimulation fatigued the extensors of both sides easily.

*Cat 119, Control.*—Except that this animal received no lead, it was treated like cat 107.

The ease with which the muscles were fatigued in the "leaded" animal and the rapid rise of threshold on both sides are evidences that the circulation of this animal was poor. Nevertheless, the threshold of the right side was somewhat higher than that of the left except in two instances, when fatigue was setting in rapidly. The constant threshold in the control is noteworthy.

EXPERIMENT 5.

*Cat 131, "Leaded."*—Lead was given intratracheally. The weight placed on the right forepaw was 80 Gm. The animal was exercised for a period of fifty-five days (16 miles). The body weight fell from 3 to 1.8 Kg. This animal used the forelimbs to a limited extent in the drum. It sprang across the drum, exerting almost its entire effort with the hind limbs. As far as could be determined from threshold and action currents, there was no diminution in the threshold of the weighted side.

This animal showed good extension of the weighted limb before the operation, and therefore the absence of any increase in threshold is not surprising. In fact, it confirms a certain relationship between the threshold of the muscle and its clinical appearance.

## COMMENT

The original purpose of these mammalian experiments was not accomplished. Our object in this study was to localize the lesion of palsy by producing paralysis and then to obtain action currents from muscle and nerve. Only toward the end of the investigation, however, was technic developed by which such action currents could be obtained without artefacts. At this time the "leaded" animals were in a poor condition, and none were really fit subjects for such an experiment. It is clear from these experiments, however, that extensor weakness follows muscular work. Both limbs performed approximately the same movements, but the muscles of one had to do more work because of the attached weights. Consequently, this suggests that lead injury is caused by muscular activity and fatigue.

Proper appreciation of these experiments requires a brief consideration of the chemical relationship between lead in the body and the products of muscular activity. In this laboratory, both Fairhall [19] and Minot [20] have shown that lead is deposited in the bones as insoluble lead phosphate, but when mobilized it is transported by the blood stream as the triple phosphate. Any bodily change which tends to disturb the acid-base equilibrium—for instance, acidosis—liberates lead from the bones and greatly increases the quantity in circulation.[21] This was illustrated by the increased excretion of lead by both patients and animals when they received a diet low in calcium and were treated with either ammonium chloride or acid. Acute respiratory infection seemed to produce the same results in animals. Lead probably acts in this way because the phosphate is very soluble in acids, especially in lactic acid

19. Fairhall, L. T., and Shaw, Charlotte P.: Lead Studies: X. The Deposition of Lead Salts, J. Indust. Hyg. **6**:159 (Aug.) 1924.

20. Minot, A. S.: Lead Studies: V. A, B, C. Lead Distribution in the Organism, J. Indust. Hyg. **6**:125, 137 and 149 (Aug.) 1924.

21. Minot, A. S., and Aub, J. C.: Lead Studies: XII. The Mechanisms for Storage and Excretion of Lead, to be published.

which is liberated in large amounts during muscular activity, particularly during fatiguing exercise.[22] Therefore, when lead phosphate circulates through muscle undergoing vigorous exercise, it must be dissolved to a considerable extent by the lactic acid and thus be converted to lead lactate.

If such a soluble lead salt as the lactate comes into contact with a cell, it can unite with the inorganic phosphate present at the surface [23] and form insoluble lead phosphate and free lactic acid. In work already reported,[9] it was suggested that the precipitation of this insoluble lead salt, which is accompanied by the liberation of free acid and the removal of buffer phosphate, changes the colloidal state and the properties of the red cell surface. There is considerable evidence that this also occurs in muscle. Clinical observation has established the fact that the muscles paralyzed are those which are most used. As far as is known, only muscle and not nerve becomes fatigued, and experiments in vitro have demonstrated that lead does not interfere with the function of isolated nerve, whereas it does greatly affect muscle. This change in muscle function is preceded by an alteration of the surface permeability, and it is therefore probable that lead acts on muscle just as on red blood cells by changing the permeability of the surface.

Thus these considerations afford a possible explanation of the development of lead palsy: Lead is transported by the blood as an insoluble phosphate in colloidal state. In regions of muscular activity this is dissolved by the excess lactic acid which diffuses from fatigued muscle cells and is converted into lead lactate. As the soluble lactate comes in contact with inorganic phosphate at the surface of muscle cells, the lead is reprecipitated as insoluble phosphate—a reaction dependent on the relative concentration of lactate and phosphate.

## CONCLUSIONS

1. Experiments with isolated nerve-muscle preparations from frogs have shown that the onset of fatigue in muscles which have been exposed to lead is much more rapid and complete than normal.

2. The contractility of "leaded" muscles is often completely lost, and recovery from fatigue is always impaired.

3. When muscles are immersed in Ringer's solution containing lead, the acidity of the solution increases markedly.

4. A change in the permeability of the surface of muscle cell after exposure to lead is evidenced by an increased diffusion of inorganic phosphate from the muscle into the surrounding Ringer's solution.

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22. Ritchie, A. J.: The Reaction of Resting and Active Muscle, J. Physiol. **56**:53, 1922. Barr, D. P.; Himwich, H. E., and Green, R. P.: Studies in the Physiology of Muscular Exercise, J. Biol. Chem. **55**:495 (March) 1923.

23. Embden and Laquer (footnote 1, tenth reference).

5. As far as can be seen from the response of muscle to nerve stimulation, lead salts seem to have no deleterious action on the conductivity of the nerve of an isolated nerve-muscle preparation from a frog.

6. In one experiment, records of action currents taken from both nerve and muscle also indicate that lead acts on muscle and not on nerve.

7. Marked weakness or even palsy develops in fatigued extensor muscles of "leaded" rabbits and cats. This was manifested by great difficulty in extending the forepaw.

8. The threshold of these weak muscles to stimulation is much higher than that of unfatigued muscles or of the corresponding muscles in control animals.

9. Neither lead nor fatigue alone causes palsy, but both are necessary to establish the condition. This is indicated by experiments in vitro with isolated nerve-muscle preparations and by the similarity between the threshold values of unfatigued muscles of "leaded" animals and the muscles of the controls.

10. Such experiments indicate that the physiologic lesion of lead palsy is in the muscle itself and that the muscles which are fatigued are most susceptible to lead paralysis.

11. An attempt has been made to explain susceptibility to lead palsy on the basis of the chemical and physiologic reactions between the metabolic products formed during muscular activity and lead as it occurs in the human organism.

# METASTATIC MENINGO-ENCEPHALIC CARCINOMATOSIS WITHOUT TUMEFACTION *

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The ordinary conception of cerebral neoplasm, whether primary or secondary, intramedullary or extramedullary, is that of a definite nodule or infiltrating mass. The expressions diffuse carcinomatosis or sarcomatosis are employed to convey the idea of extent, but there is not a suitable terminology to connote neoplasia without tumefaction. An instance of this was encountered in the course of routine examinations of neuropathologic material, and it is reported because the pathologic features are at variance with the usual concept of tumor of the brain.

## REPORT OF CASE

*History.*—A man aged 30, was admitted to the New York City Hospital on Jan. 6, 1924, complaining of headache, backache, insomnia, and nausea without vomiting, which had existed for three weeks.

The physical examination revealed bilateral papilledema with 7 diopters swelling of the disk; inflammatory changes were not present in the fundus. The patellar reflexes were absent, and the abdominal reflexes were increased. There were multiple, raised, firm nodular masses scattered through the skin of the abdomen varying from 0.5 to 2 cm. in diameter, none of which were tender. The skin covering a few of them was bluish. Some of the nodules had been present for several years. The anterior and posterior cervical, supraclavicular, epitrochlear and inguinal lymph nodes were enlarged and palpable.

*Clinical Course.*—The headache and backache increased in intensity and required morphine for relief. The backache was in the lumbar region. Three days after admission, occasional attacks of vomiting occurred, but this was not of the projectile type nor related to the ingestion of food. The temperature was normal. The blood pressure was 178 systolic; 130, diastolic. The blood chemistry did not show any retention of nitrogenous products; the urea nitrogen was 16 mg.; creatinine, 1.66 mg.; sugar, 100 mg. The blood count revealed 5,200,000 erythrocytes; hemoglobin, 95 per cent, and 12,000 leukocytes with 81 per cent polymorphonuclears.

On the sixth day after admission, there was vomiting after every meal. Kernig and Brudzinski signs were positive. The response to plantar stimulation was suggestive of a positive Babinski sign on the left but was normal on the right. A left chronic otitis media was noted. The spinal fluid was under normal pressure; it was a light yellow, with 7 cells and an increase of globulin. The Wassermann reaction was negative in both blood and spinal fluid. The urine was normal.

On the ninth day the neck became rigid, and flexion produced pain. Slight weakness was present in the right arm. A low muttering delirium developed,

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* Read by title at the Fifty-Second Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 3, 1926.

from which the patient could be aroused and induced to respond to questions. The vomiting became more frequent. Stimulation of the skin with cotton wool over the abdomen, chest, back and buttocks produced a decidedly disagreeable sensation and was complained of bitterly. A second lumbar puncture revealed an increase of globulin as the only pathologic symptom. Organisms were absent in smears and cultures.

On the tenth day the pupils were unequal, the right being larger than the left, but not any abnormalities were present in the reactions to direct and indirect light, accommodation or convergence; the movements were not impaired nor was there nystagmus. The vomiting increased until it became almost constant by the twelfth day, and food could not be retained after oral administration. The temperature remained normal.

The diagnoses of neurosyphilis, tuberculous meningitis and tumor of the brain were considered. The first was excluded on account of the absence of a history of infection, the unusual clinical picture and the negative examinations of the blood and fluid; the second diagnosis was militated against by the absence of tubercle bacilli and pleocytosis in the spinal fluid and the absence of tuberculosis elsewhere in the body. Tumor of the brain was considered as the most probable diagnosis in view of the signs of meningeal irritation, the evidence of increased intracranial pressure and choked disks, without hyperthermia.

Roentgenograms of the long bones, the spine and the skull were normal. A tumor was not visualized, and signs of increased intracranial pressure were reported to be absent by the roentgenologist.

A frozen section of one of the nodules from the skin of the abdomen showed a large tortuous nerve in the corium with an increase of the connective tissue of the endoneurium, perineurium and epineurium. The nerve was embedded in a dense connective tissue stroma that contained many collagen fibrils and an abundance of undifferentiated connective tissue cells. The diagnosis of fibromatosis of the skin was made, and origin from the neural sheath was considered probable.

The patient continued to grow weaker without any change occurring in the physical signs. On the twenty-second day, signs of bronchopneumonia appeared and death occurred on the twenty-fourth day after admission.

*Macroscopic Pathologic Changes.*—The postmortem examination disclosed a gelatinous carcinoma on the lesser curvature of the stomach just proximal to the pylorus with metastases to the peritoneum, epicardium and skin. Examination of the other thoracic and abdominal viscera did not disclose any pertinent pathologic change. Death was the result of terminal bronchopneumonia.

The conformation of the brain was normal. There was moderate venous engorgement of the pial vessels. The leptomeninges covering the convexity and base were slightly thickened and opaque. Sections of the brain failed to disclose any microscopic tumor nodules in any part. Owing to the anxiety of the attending medical personnel to locate the supposed tumor, this sectioning was thorough and when the specimen came into the hands of the neuropathologist it consisted of a series of thin longitudinal sections; therefore I am not able to give any information concerning the presence or absence of internal hydrocephalus. The ependyma was normal on gross examination. After the autopsy it will be noted that an explanation for the choked disks was not apparent from the macroscopic examination, although the low grade meningitis noted could possibly have accounted for the headache and other meningeal symptoms.

*Microscopic Pathologic Changes.*—Distention of the lymph spaces of the pia mater was present. This was uniform in all parts examined: frontal, occipital, temporal, midbrain, pons and cerebellum. In addition to the edema there was infiltration of the pia mater with lymphocytes, plasma cells and neoplastic epithelial cells of the character typical of gelatinous or so-called colloid carcinoma. The cells were large and round or oval with both pyknotic and hypochromatic nuclei. In some cells the nuclei were centrally located, while in others they were eccentric, in many instances being displaced to the periphery and flattened. The cytoplasm was in some cases deeply stained and basophilic; in others it was

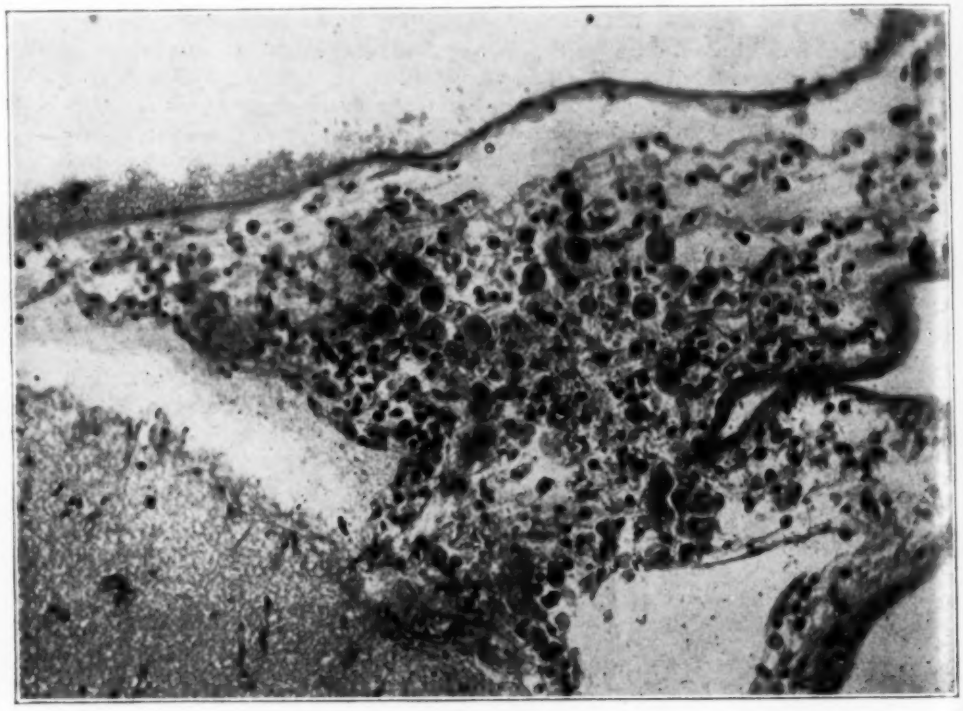

Fig. 1.—Diffuse distribution of carcinoma cells together with lymphocytes and plasma cells in the lymph spaces of the pia-arachnoid. Low power.

stained faintly or not at all and contained large, clear globular vacuoles. Mitoses frequently were encountered (fig. 1).

There were some relatively large areas of hemorrhage in the occipital lobes associated with extensive destruction of tissue. Surrounding these areas was distortion of the normal architecture of the cortex, the ganglion cells being elongated and atrophic. Gitter cells and rod cells were present. In a few portions of the occipital cortex there were areas of granulation tissue extending from the surface into the depths of the cortical tissue. Tumor cells, mingled with plasma cells and lymphocytes, were present in the perivascular spaces of numerous areas examined. This feature was especially prominent in the midbrain (fig. 2).

The cranial nerves at their points of emergence were all surrounded by exudate containing tumor cells and those examined, the optic, facial and auditory, had tumor cells within their substance. In the optic nerve, the interstitial connective tissue of the endoneurium and perineurium was increased to a degree sufficient to constitute a well defined interstitial neuritis, and tumor cells were present around some of the blood vessels. In the case of the seventh and eighth nerves, rows of large vacuolated epithelial cells were present within the substance of the nerves, and widespread destruction of the nerve fibers had taken place, but marked proliferation of the perineurium had not occurred.

Sections of the stomach revealed typical gelatinous carcinoma, with extensive destruction of the mucosa and extension into the musculature. In the location

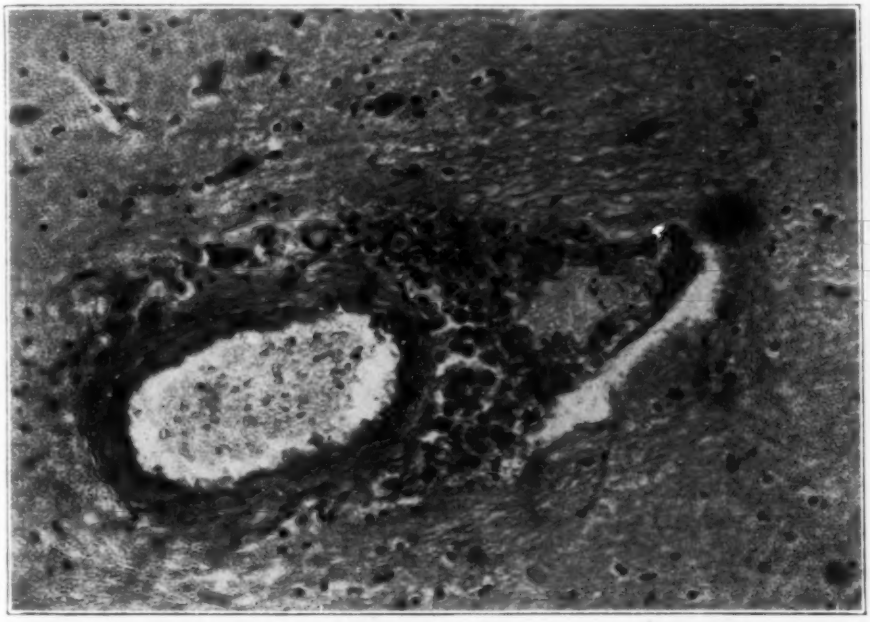

Fig. 2.—Carcinoma cells in a Virchow-Robin space surrounding a blood vessel in the left cerebral peduncle.

of the nerves between the circular and longitudinal muscle layers were groups of large vacuolated cells containing mucin. The nerve fibers were mostly destroyed. This localization of tumor cells in the wall of the stomach suggested that the metastases had spread by way of the epineural lymph channels.

On account of the history of the existence of nodules in the skin of the abdomen several years previous to the final illness, together with the extensive productive reaction on the part of the connective tissue within and around the nerves in the skin, it was believed that some of the skin metastases had occurred in preexisting fibromatous nodules. A nodule removed from the skin of the abdomen at necropsy revealed, in addition to the features noted in the biopsy specimen, large vacuolated epithelial cells containing mucin in the sheath of the nerve.

COMMENTS

A case with nearly identical clinical symptoms, duration of illness and distribution of meningeal and encephalic foci has been reported by Boyd.[1] In his case the tumor was a melanoma. In addition to the cellular accumulations in the subarachnoid space and the perivascular and perineural prolongations, there were similar collections of cells in the skin and left kidney.

Fried[2] reported a case, in Dr. Harvey Cushing's service, which resembled this one in age, duration of illness and distribution of the foci in the meninges and brain. In that case, however, necropsy was limited to the head; therefore, in the opinion of the author, there were "no irrefutable criteria to disprove that it might be of metastatic origin." In addition, one nodular mass was discovered just below the cortex of the first left temporal convolution that measured 1 by 0.5 cm. Fried regarded the tumor as a round cell sarcoma originating from the adventitial cells of the blood vessels.

Lewis[3] has recorded a case with sudden onset of symptoms, diagnosed as catatonic dementia praecox and later as epidemic encephalitis, in a man aged 27. The duration of the illness was about two months. There was an absence of gross tumors in all the organs, but microscopic examination of the brain revealed generalized miliary carcinomatosis.

This case may be added to those already recorded as an illustration of brain neoplasm of meningo-encephalic distribution without macroscopic tumefaction. The nature of the neoplasm was a metastatic gelatinous carcinoma, the primary site being in the gastric mucosa. The extension from the primary site in the gastric mucosa would appear to have been by way of the perineural lymphatics. The basis for this opinion lies in the fact that metastases were observed in the zone occupied by nerve fibers in the stomach wall, in the perineural sheaths of the skin nerves, in the subarachnoid space, in the perivascular lymph spaces of the encephalon and within the substance of the optic, facial and auditory nerves.

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1. Boyd, William: Diffuse Tumors of the Meninges, Am. J. Path. **1**:583 (Nov.) 1925.

2. Fried, B. M.: Sarcomatosis of the Brain, Arch. Neurol. & Psychiat. **18**: 205 (Feb.) 1926.

3. Lewis, N. D. C.: An Unusual Manifestation of Miliary Carcinomatosis of the Central Nervous System, Am. J. Psychiat. **82**:171, 1925; abstracted in Am. J. M. Sc. **171**:460 (March) 1926.

# PATHOLOGIC ANATOMY IN THE HYPOPHYSIS CEREBRI IN WILD ANIMALS*

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The attention of an observer is attracted to diseases of the endocrine system by unmistakable abnormality of development in young individuals, by a group of signs of variable definiteness or by autopsy observations. Except in certain gigantic states and sexual dystrophies, changes in anatomy and physiology of the pituitary body do not express themselves in a clear-cut manner. Acromegalic and genital alterations, while fairly clear in the human being, are not by any means so readily determined in the lower animals. This is especially true of wild varieties. In a reasonably complete review of the literature I did not discover a satisfactory case of pituitary disease in wild animals. There are numerous references in the literature to inflammation, strumas and tumors in the domestic animals, and there is a considerable volume of writing about the state of the hypophysis during pregnancy and hibernation. However, the relationship of pathologic to clinical conditions is not clear, and specific abnormalities of structure of the pituitary do not always seem to give rise to the same clinical manifestations. With this handicap, interpretations of both sides of the matter are difficult, and the citation of new cases may be of profit. A few observations of what might be termed "raw material" are therefore offered on the pathology of wild animals as seen at the Laboratory of Comparative Pathology of the Philadelphia Zoological Society. During the past three years six animals showing some abnormality in or around the pituitary body have come to autopsy. In two of these cases these lesions seemed to be the principal cause of death. The records are given in full. The incidence and the nature of these lesions are interesting enough, but their significance can be better evaluated by a consideration of histories, related pathology and the possible relationship to other clinicopathologic states. Each condition that might be related with the pituitary is discussed briefly.

The animals concerned in this report belong to the Primates (2) and Ungulata (4). One of the monkeys is Asiatic and the other South American. The ungulates are an Indian buffalo, an oryx, a springbok and a wart-hog. The last had been in the collection only eight months, but the other five had been on exhibition for from three to

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* From the Laboratory of Comparative Pathology of the Philadelphia Zoological Society.

* Read at the Fifty-Second Annual Meeting of the American Neurological Association held at Atlantic City, June, 1926.

seventeen years. All the specimens could be classed as adult or mature, that is, potentially fertile animals. They were to all appearances normally constructed. Five of the six were females. All but the oryx were exhibited with mates that made conjugation possible, but only one animal, the buffalo, had borne young. This beast gave birth to a calf eight months before death; she had had three young in the four and one-half years of her exhibition.

Notes as to the growth of the specimens are not available. The condition of the bones is of some importance. Two carcasses are described as having normal osteology. The skeleton of the Indian buffalo, which showed the pituitary adenoma, was apparently normal, and there did not seem to be hypertrophic change in the bones comparable to acromegaly. In this regard it must be stated that the observer has seen only one other skeleton of this species, but the general configuration was comparable to that of other specimens of the genera *Bos* and *Bison*. The springbok had an acute necrotizing osteitis of the cranial bones which apparently emanated from a dental root abscess. The South American monkey had osteomalacia. This degenerative condition of the bone is common with these monkeys, is due to incorrect feeding and perhaps to restraint, but does not seem to have any relation to the pituitary body, if one may judge by the fact that gross inspection of this organ in some dozen cases did not reveal abnormality.

Some observers believe that the thyroid body is closely related to the pituitary body, while others have failed to confirm a compensatory function. Blair Bell describes a distinct prominence of basophilic cells of the anterior lobe in exophthalmic goiter, and Branchli notes a decrease of chromophilic cells and an increase of chromophobic cells in endemic goiter. Various types of thyroid hyperplasia occur in wild animals, notably in the carnivores, but there have not been gross alterations in the pituitary body, and one of the goitrous specimens described here did not show any histologic peculiarity of the hypophysis. The buffalo that is described here had a small colloid goiter. Its pituitary tumor was made up of basophilic and eosinophilic cells.

Abnormality was not noted in the suprarenal, ovary, thymus or pancreas. Considerable attention was paid to the uterus, which was, with one exception, apparently normal in the animals included in this report. The single exception, the oryx, had a sarcoma nodule and an old, small calcified fibroid. Pituitary adiposity has been discussed by veterinarians, and some satisfactory cases are recorded. None of the specimens concerned in this report seemed to be excessively fat and sluggish, nor did they show secondary sex characters of the opposite sex. Observations in this regard must of course have limited value, since one is not sufficiently familiar with configurations and habits to draw conclusions. There are no data on simple diabetes and tolerance of sugar. Renal disease is not more common in these six animals than in the general autopsy list.

A survey of the foregoing analyses of the possible evidences of pituitary disease and of pathologic conditions sometimes associated with it, reveals that in these six instances of alterations in and about the hypophysis in wild animals, there was not a definite clinical state, and peculiar morbid lesions were not found in relationship to it. It certainly seems, from the condition of the beasts and from their long average exhibition period, that the pituitary lesion affected their health little until mechanical damage reached an advanced degree. Until more is known about the pituitary body in wild animals, attempts at conclusions would be unwise, further than to state that fatal mechanical injury has been seen. The greatest injury was done by ulceration of bone and by hemorrhage, at least in the three cases in which these conditions were pronounced. The material is reported for the sake of record and to illustrate the types of lesions discoverable in the wild animal.

CASE 1.—A female *Oryx leucoryx* that had been in the garden from April 24, 1909, to April 22, 1926, had been in good health until about June, 1925, when it began to get thin. For two weeks prior to its death it lay down most of the time and could barely get up. At autopsy it was found that this condition was caused by a sarcomatosis, the origin of which was probably in the intestinal or mesenteric lymphatic tissue. There were partly calcified parasitic masses in the middle lobes of both lungs; there was recent acute hepatitis, a calcified fibrosis of the uterus and trichocephalus in the colon.

The pituitary lay in a sharply outlined elliptic sella, the base of which was unevenly marked, but was not necrotic, porotic or ulcerated. The body itself was rather smooth on its exterior surface; it was deep pink with rather prominent small vessels. It measured 18 by 15 by 12 mm. At the posterior extremity where the dura was reflected away was a row of gelatinous or edematous swellings, 1 or 2 mm. across which suggested small cysts in the capsule. The organ was otherwise solid and firmer than normal. Section showed that the mass of the gland was gray-red and indefinitely laminated. The infundibulum could be seen, but a separation of the epithelial and nervous tissue was not distinct. In the anterior-inferior part of the organ, anterior to the infundibulum, entirely embedded in the organ, was an irregularly spherical, pearly gray, glistening, homogeneous, cartilaginous mass, 3 by 4 mm., sharply surrounded but not encapsulated.

Anteroposterior section showed a large, irregular distal lobe, a flattened and stretched-out tuberal section and a broken part of the nervous section. In the infundibular area there was an abnormal construction surrounded by a thin portion of the tuberal lobe and by a layer of flat and low cuboidal, deeply staining cells. The cavity contained a deeply basic staining, amorphous, granular, fragile material (this corresponds to the cartilaginous nodule described in the notes on the gross examination). In the infundibular portion there were thin walled spaces of irregular size lined with flat or cuboidal, deeply staining cells and containing the same material. There were other smaller spaces, which contained bits of eosin-staining material, probably colloid. There were transitions between the two, which suggested that they were related. The tuberal portion consisted of compressed strands and groups of cells, chiefly basophilic.

The epithelial portion showed distinct eosinophilic predominance. The groups of glands were solid, practically without lumen; the cells were elongated, cylindrical and thinned out.

The whole gland was much congested, with occasional small areas of hemorrhage, or at least, blood in places in which it did not seem to have a conducting wall.

The pathologic diagnoses included colloid cyst in the infundibulum, inspissated colloid in the tuberal portion, excess of acidophilic cells and congestion of the distal portion.

Case 2.—A female Pallas wart-hog *(Phacochoerus pallasi)* that was in the garden from June 16, 1925, to Feb. 8, 1926, had been off its feed for a few days before its death, but nothing in particular was noticed. The body was in excellent condition when autopsy was performed. Dissection of the head showed large blood clots in the pharynx and in both nasal cavities. These clots seemed to emanate from the right pharyngeal wall, which was occupied at the top by a firm, flat, but nodular mass, closely applied to the bone. Removal of the brain showed it to be in good condition, including the pituitary body. There were clots in the supra-orbital and middle compartments of the frontal sinuses. The floor of the sella was occupied by a dull red tissue suggestive of delicate placental tissue. Apparently this had eaten away the body of the sphenoid and the under surface of the basilar process of the occiput. It was found to have extended to the pharyngeal vault by growing through the anterior lacerate foramen. The exact point of the massive hemorrhage was not discoverable. It may have been from a large vessel of the pharyngeal wall, or it may have been caused by rapid oozing from the main mass which might have involved the adjacent cavernous sinus. Both nasal spaces contained a large blood clot and there was free blood in the pharynx and some in the trachea.

The observations at autopsy were: generalized edema, including the peritoneum, pleura and pericardium; calcified nodules in the biliary tract and liver with some recent acute abscesses; acute splenic tumor, mild acute catarrhal enteritis and cloudy swelling of the kidney.

The measurements of the pituitary body were 13 by 10 by 5 mm.

The floor of the sella turcica was not ulcerated, but was roughened. The dull red, felt-like tissue between the pituitary and the bone seemed to consist of large and small vessels with good walls, all surrounded by free blood. The thickness and extent of this vascular mass were definitely greater than those with which I am familiar. Grossly, the tumor might be looked at as a flat angioma, but this is not borne out by the histology. The cause of this hemorrhage and of its penetration to the pharynx is not clear. The pharyngeal wall at the site of the nodule showed a distinct hyperplasia of the mucoserous glands, a tortuosity and irregularity of their ducts and a distinct hyperplasia of the lymphoid tissue. There was not anything that would ordinarily explain the prominence in the pharynx of the hemorrhage.

Section showed the complete pituitary body except a portion of the stalk. The nervous portion was fairly rich in cells, but especially noteworthy was the large amount of old blood pigment in the mass. This did not seem to have destroyed any tissue. The stalk was well surrounded by the tuberal portion which consisted of small, rather compact, deeply basophilic cells. The cellular portion of the infundibular group was basophilic, and contained a few areas of condensed colloid. The distal portion was about equally basophilic and acidophilic, although these cells were not uniformly distributed. There were few

chief cells. The groups of cells were irregular, and many fields were without a distinct acinus construction. The pathologic diagnosis was old hemorrhage in the nervous portion of the pituitary body.

CASE 3.—A male white-throated cebus *(Cebus hypoleucus)* that was in the garden from Feb. 13, 1923, to Dec. 23, 1925, had been weak in the legs for two years. He did not have osteomalacia, as so many of these animals do. At autopsy he was found to have chronic bronchiectasis and patches of atelectasis, marked constipation, acute catarrhal enteritis and acute follicular splenitis.

The pituitary body seemed little enlarged, but there was hemorrhage between it and the bone. The floor of the sella had disappeared on one side, the cancellous tissue had separated, and free blood was present. On section, bone absorption and erosion could be found. The marrow was slightly hyperplastic and showed the position of old hemorrhage and excessive pigmentation. Free blood in small quantities was seen next to the bone.

The nervous portion was not extensive but it was much congested. The infundibular portion was extensive and irregularly distributed around the nervous portion. The nuclei of the cells were clear and their cytoplasm was indistinct. The cells seemed undifferentiated and suggested tumor cells. The observer was not sure that he could recognize a tuberal portion, at least distinctly separated from the distal portion. What might be tuberal, by reason of spaces lined with chromophilic cells, merged with the infundibular portion. The distal portion consisted of irregular groups, chiefly chromophilic. The observer believed this to be a hyperplasia of the infundibular portion of the hypophysis, but could not state that it was an adenoma. This could not have been a menstrual reaction because of the sex. The infundibular area is normally not especially large in monkeys.

CASE 4.—A female springbok *(Gazelle euchore)*, weighing 35 pounds, was received at the garden on Sept. 3, 1920, and died on Jan. 5, 1924. An autopsy was performed on the day of its death. The history showed that the animal was in good condition until December 15, when it was found drooping and not eating. The stools were soft. This condition continued until death, although at times the appetite returned for short periods.

Autopsy showed necrotic, punched-out ulcers of the stomach, probably connected with the caries of the molar teeth, with peridental ulceration and necrotizing osteitis and cellulitis; chronic parasitic enteritis with patches of calcification in the wall and an acute hemorrhagic exacerbation; cloudy swelling of the liver, calcareous nodules in the lungs and a hemorrhagic infarct in the left lung. Streptothrical forms were found in the gastric lesions.

The pituitary body was irregularly globular, varying around 1.5 cm. in different dimensions. It was deep red, irregularly outlined and hemorrhagic.

A section was made which consisted of three divisions in about the following proportions: epithelial lobe, 5; infundibular section, 3; nervous section, 1. The epithelial lobe was rich in blood, and the groups of cells were somewhat compressed by the capillary congestion. The basophilic cells were compressed and seemed to contain vacuoles. The lumen of the spaces surrounded by basophilic cells, when it was distinguishable, contained neutrophilic amorphous material in small quantities. The oxyphilic cells and others, the protoplasm of which did not stain, were more numerous than the basophilic. They, too, were probably vacuolated. Colloid cysts and real adenomatous structures were not present.

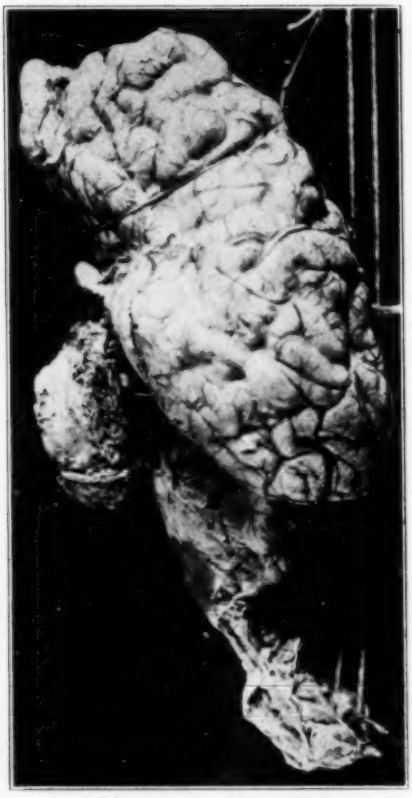

Fig. 1.—Lateral view of the brain of an Indian buffalo, showing the size of the pituitary mass.

Fig. 2.—Inferior surface of the brain of an Indian buffalo, showing the extent of the spread of the tumor and the dislocation of the optic chiasm.

The tuberal portion showed chromophilic, that is, basophilic, cell groups without lumen. It was rich in blood. Eosinophils were inconspicuous or absent.

The nervous portion showed some granular disintegration and much congestion.

Fig. 3.—Pituitary adenoma in an Indian buffalo, showing acinus and hemorrhagic areas.

This seemed to be a congestion of the distal lobe with great prominence of the "a" and chief cells and degeneration of the nervous lobe.

CASE 5.—A female bonnet macaque *(Macacus sinicus)* that was in the garden from Nov. 24, 1915, to Oct. 8, 1923, had apparently been in good health, but was found dead. The body was in excellent condition.

Autopsy showed a mucopurulent nasopharyngeal sinusitis with infiltrative tonsillitis and a peritonsillitis; a mucopurulent bronchitis and bronchopneumonia, a process which was apparently caused by a staphylococcus and the influenza bacillus; general lymphadenitis, acute parenchymatous nephritis, acute diffuse splenitis, cloudy swelling of the liver, a recent thrombus in the left ventricle, acute erosion of the stomach, an esophageal ulcer and a cystic prom-

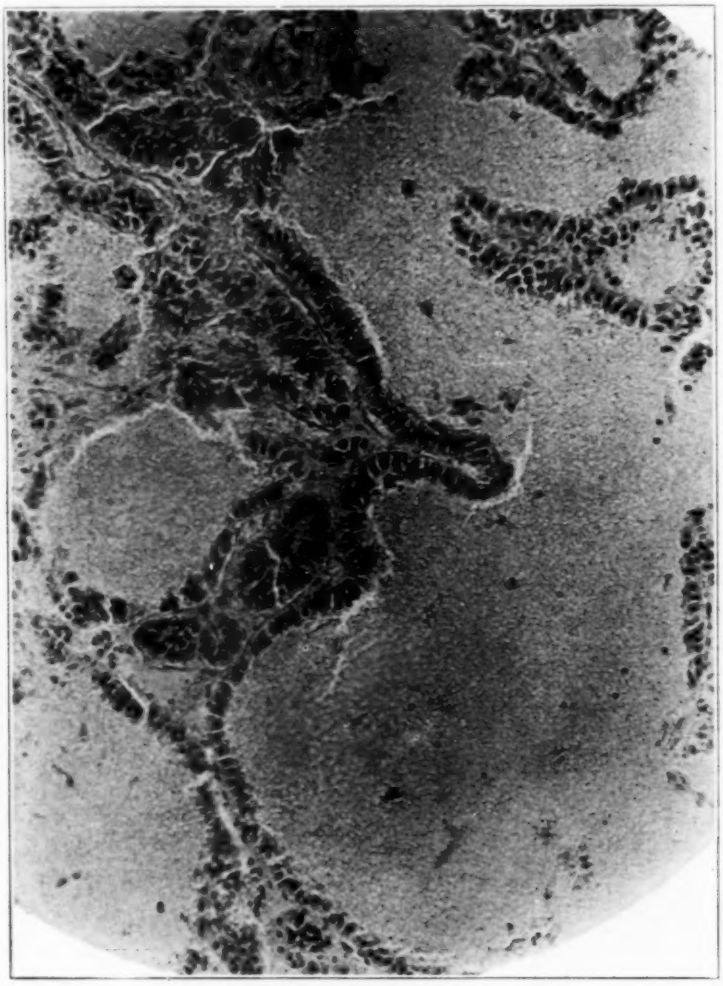

Fig. 4.—Pituitary adenoma in an Indian buffalo, showing a papillary cyst-adenomatous area.

inence of an enlarged pituitary body. Between the anterior lobe and the optic commissure there was a 2 mm. clear cyst arising from the stalk of the hypophysis. Section unfortunately failed to show this cyst. In structure this pituitary corresponded closely with the descriptions by Tilney and by Stendell.

The tuberal portion was not clearly separated from the distal lobe and could only be separated by the appearance from one section to another of eosinophilic cells. Chromophilic cells greatly outnumbered chromophobes.

The infundibular portion was quite distinct. It did not contain colloid, while there were small masses of this substance in the distal portion. This was probably a normal pituitary body.

CASE 6.—An Indian buffalo *(Bos bubalis)* that was received at the garden on Sept. 25, 1918, died on April 4, 1923. It was a female, weighing 1,030 pounds (467 Kg.), an increase of 140 pounds (63.5 Kg.) during its life here. During

Fig. 5.—Pituitary adenoma in an Indian buffalo, showing areas of solid adenoma and hemorrhage.

the four and one-half years at the garden this animal had borne three healthy young. It was in excellent condition until a few days before its death, which was apparently due to a large hemorrhage in the pharynx. Clot and free blood were found in the pharynx and in the air passages. The blood apparently came from an ulceration of the pharynx and from an erosion of the basilar portion of the occiput and of the sella, caused by a large, blood red, soft tumor. The

optic tract was dislocated forward. The mass extended backward beyond the crura almost to the foramen magnum. Its dimensions were 4.5 cm. anteroposteriorly, 4 cm. laterally and 2.5 cm. in depth (figs. 1 and 2). Autopsy revealed, in addition to the foregoing observations, bronchopneumonia with passive congestion and cloudy swelling of the liver, an acute enteritis, colloid goiter and cloudy swelling of the kidney.

Section showed three kinds of tissue: a finely fibrillar or homogeneous background or framework in which there were dilated blood spaces containing whole or degenerated blood, cellular groups in strands and an acinus formation, almost invariably surrounded by a condensation of connective tissue sufficient to be called a basement membrane. Some of these acinus groups had suffered by hemorrhage, cells being totally destroyed or compressed to a narrow rim (figs. 3 and 4). There had been a great deal of hemorrhage all over the growth, judging by the amount of pigment and the shape of the cells composing the cellular part of the mass. If compressed they were flattened out; if growing on a basement membrane, they were cylindric; if growing within the mass, they were round or polyhedral. The protoplasm took eosin well, and the nucleus stained deeply and probably contained some distinct masses of chromatin. A vacuolated nucleus was not uncommon. At three places small irregular groups of much larger cells resembling malignant cells were seen. In the four sections at different levels it was impossible to recognize the three divisions of the pituitary body. Practically all the nuclei were chromophilic with a distinct cytoplasm, however; therefore they were of the "a" type. Two areas of the papillary cystadenomatous type were found (fig. 5).

Because of the solid nests, the papillary areas and the groups of large hyperchromatic cells, this growth was called an adenoma.

# METASTATIC TUMORS OF THE BRAIN

## A CLINICAL STUDY OF TWELVE CASES WITH NECROPSY *

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During recent years a number of cases that have been poorly defined clinically have come under observation in the neurologic service of Mount Sinai Hospital, in which subsequent studies at necropsy have in many instances disclosed unsuspected metastatic tumors of the brain. A survey of this clinical material revealed the fact, which we regard as highly significant, that in only a limited number of instances was the neoplastic character of the disease process recognized, and that still less frequently was the metastatic nature of such lesions considered among the diagnostic possibilities.

A review of leading textbooks of neurology [1] as well as a fairly thorough study of the literature disclosed a striking lack of satisfactory discussions on the subject of the clinical and diagnostic features of metastatic tumors of the brain. The more important contributions bearing on the clinical aspects are given here,[2] but an analysis of these articles

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* Read before the New York Neurological Society, March 4, 1926.

* From the neurologic service and the neuropathologic laboratory of the Mount Sinai Hospital.

* Aided by a grant from the Emanuel Libman Fellowship Fund.

1. Oppenheim, H.: Lehrbuch der Nervenkrankheiten, Berlin, 1923. Lewandowsky, M.: Handbuch der Neurologie, Berlin, 1912.

2. Buchholtz: Carcinome des Zentralnervensystems, Casuistischer Beitr., Monatschr. f. Psychiat. u. Neurol. **4**:183, 1898. Seifert, E.: Ueber die multiple Carcinomatose des Zentralnervensystems, Arch. f. Psychiat. **36**:720, 1903. Fischer, O.: Zur Kenntnis des multiplen metastatischen Carcinoms des Zentralnervensystems, Jahrb. f. Psychiat. u. Neurol **25**:125, 1904-1905. Babinski, Jarkowski and Bethoux: Sarcome melanique du cerveau à foyers multiples, consécutif à une neoplasie de la choroide de la même nature, Rev. neurol. **29**:331, 1922. Meyer, E.: Zur Kenntnis der Carcinomatosen des Zentralnervensystems, insbesondere der diffusen Carcinomatose der weichen Häute, Arch. f. Psychiat. **66**:283, 1922. Gans, A.: Cancer Foci in the Brain, Nederl. Tijdschr. Genessk. **67**:1043, 1923. Morse, M. E.: Two Cases Illustrating the Pathologic and Psychiatric Aspects of the Carcinomatous Metastasis of the Central Nervous System, J. Nerv. & Ment. Dis. **58**:409, 1923. Weiman, W.: Ueber melanotische Geschwuelste im Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **85**:508, 1923. Lyter, J. C.: Multiple Adenomacarcinoma of the Brain, M. Clin. N. Amer. **7**:1583 (March) 1923-1924. Toulose, E.; Marchand, L., and Pese: Troubles mentaux

is not attempted, since the observations recorded are not made on numerically convincing material.

In undertaking a critical review of a large group of cases that had been well observed clinically and verified anatomically, we endeavored to establish, if so warranted by facts, a uniformity in the clinical picture as an aid in the diagnosis of metastatic tumors of the brain. Early in our study we observed that the main diagnostic difficulty is to be found in the fact that the great majority of primary malignant foci are so well masked as not only to allay any suspicion of their existence but even to defy any attempt to disclose their presence.

With this in mind and for the purpose of a more comprehensive presentation of the clinical records, we have arranged our cases in the following groups: (1) cases showing unsuspected and no apparent primary malignant tumor outside of the central nervous system (cases 1 to 4); (2) cases showing no detectable primary neoplasms, though circumstantial evidence indicated the existence of such (cases 5 and 6); (3) cases in which there was a history of a previous removal of a primary malignant lesion, but in which the delayed appearance of cerebral manifestations undermined the suspicion of a relationship existing between the primary malignant focus that had been removed and the cerebral symptoms that had developed later (cases 7 to 9); (4) cases in which the neoplastic character of the lesion of the brain was recognized, but in which its metastatic nature was not identified (cases 10 and 11); (5) cases in which the cerebral manifestations appeared late in the clinical course as a terminal event, and presented no neurologic problems (case 12).

## REPORT OF CASES

### GROUP 1

CASE 1.—*Cerebral symptoms of three months' duration, with acute onset and severe manifestations of increased intracranial tension. Disjointed, disseminated neurologic signs. Terminal psychosis. Rapid decline. Death without operation. Necropsy: Multiple metastatic carcinomas in cerebrum and cerebellum.*

*Clinical History.*—S. A., a manufacturer, aged 44, married, was admitted to the Mount Sinai Hospital, Aug. 11, 1923, complaining of headache and pain in the legs. He was said to have had grip five months previously. The present illness began three months prior to admission, when he began to complain of pain in the left leg and of severe headaches. One month later, the headache became associated with frequent attacks of vomiting. About this time he had had some dimness of vision, also an occasional myoclonic twitching of the abdomen and

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symptomatiques de metastases cancereuse encéphaliques, Encéphale **19**:414 (July-Aug.) 1924. Overhamm, G.: Jackson-Epilepsie auf Grund von Gehirnmetastasen eines primaeren Schilddrüsencarcinoms, Ztschr. f. d. ges. Neurol. u. Psychiat. **98**:755, 1925. Neubürger, K., and Singer, L.: Ueber reactive Veraenderungen in der Umgebung karzinomatoser und sarkomatoser Hirntumoren, Virchows Arch. f. path. Anat., 1925, p. 255.

a tendency toward drowsiness. More recently, he had had a convulsion, jacksonian in character, involving the left side, accompanied by loss of consciousness. It was followed by the development of stiffness in the left hand. The next change occurred two weeks later, when a state of relative comfort was interrupted by an abrupt decline in the condition. He grew weak, developed thickness of speech and some bladder disturbance, manifested psychic changes and passed into a state of semistupor.

*Examination.*—On admission, the patient, who was poorly nourished, was found in stupor from which he could be aroused only with difficulty. In a few short semilucid periods he appeared to be irrational. Percussion tenderness was elicited over the left parietal region of the skull; there was bilateral papilledema with hemorrhages and exudates about the nerve heads; the pupils were regular, equal and reacted well to light and in accommodation. There was impairment of left conjugate movement of the eyes; the tongue deviated to the left; the left upper deep reflexes were more active than the right, and the knee and Achilles reflexes could not be elicited. The left abdominal reflexes were absent. There was complete flaccid paralysis of both lower extremities with spastic paralysis of the upper extremities, the weakness being more pronounced on the left side. Sensory and other finer tests were unsatisfactory for lack of cooperation. Examination of the abdomen and thorax failed to reveal any palpable masses or areas of tenderness. Some bleeding was noted from the rectum, but on careful inspection no cause for it could be found; it was thought to be due to trauma caused by insertion of a rectal tube. Lumbar puncture yielded clear fluid under markedly increased pressure with 12 lymphocytes per cubic millimeter. The blood and spinal fluid Wassermann tests were negative, and the results of the blood chemical determinations were within normal limits. Examination of the urine revealed a trace of albumin and a few white blood cells. Roentgen-ray examination showed mild spondylitic changes. The blood pressure was 140 systolic and 90 diastolic. A white blood cell count showed 18,400 cells with 78 per cent polymorphonuclear cells and 22 per cent lymphocytes.

*Course.*—The patient declined steadily and rapidly. Periods of restlessness with hallucinatory episodes were succeeded by a state of stupor. Marked emaciation and flaccid paraplegia developed, death occurring eighteen days after admission. The disseminated character of the signs suggested multiplicity of lesions and, in the face of an afebrile course and negative serologic tests, the diagnosis of metastatic carcinoma was considered.

*Necropsy Report.*—Gross Anatomy (autopsy limited to the head): The dura was normal. The pia-arachnoid showed no thickening, adhesions, or clouding. The gyri were markedly flattened. On palpation, several nodules, varying in size and of firm consistency, were felt mainly in the left cerebral hemisphere. On incision several masses were seen, well demarcated from the adjacent brain tissue. They were granular in appearance and cystic in some parts. One of the nodules was at the frontal pole of the left cerebral hemisphere, measuring 1 by 2 cm.; another was in the posterior portion of the left frontal lobe near the dorsomedian fissure, measuring 2 by 3 cm.; a third was in the parietal lobe, and one in the occipital lobe, about 3 cm. in long diameter, traversing almost the entire length of the occipital lobe. In the right hemisphere only one small nodule was seen in the island of Reil. In the cerebellum, almost the entire vermis and the adjacent parts of the hemisphere were replaced by a tumor mass, about 4 by 5 cm. in diameter. (fig. 1).

Microscopic Anatomy: Sections of the neoplastic nodules in the cerebrum and cerebellum showed throughout a uniform histologic picture as to character of

cells and their arrangement. The cells were epithelial and squamous in type, and were flattened against one another. They presented vesicular nuclei, rich in chromatin material, and with numerous mitotic figures. In other places the cells assumed a reticular or syncytial character (fig.2).

*Diagnosis.*—The condition was diagnosed as metastatic squamous-cell carcinoma of which the primary seat was undetermined.

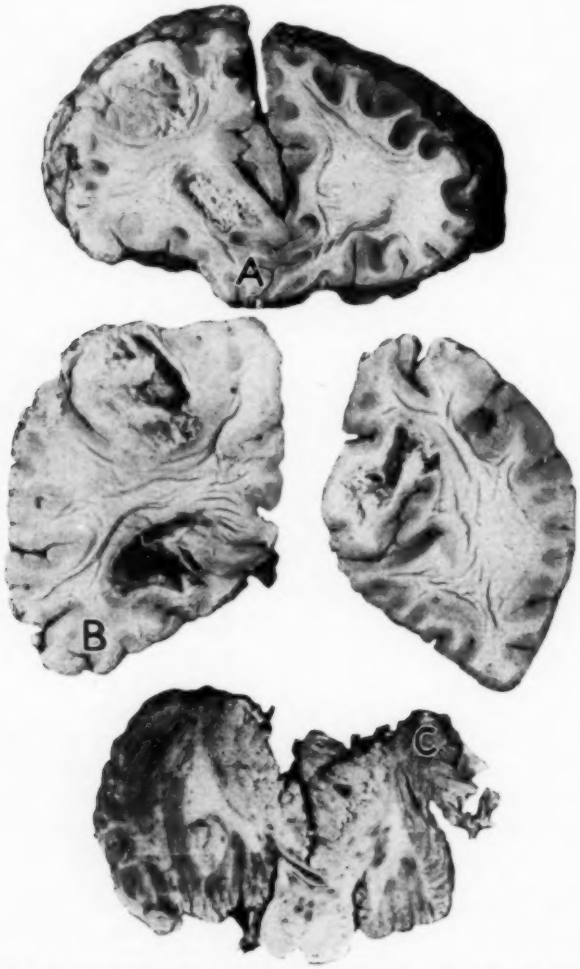


Fig. 1 (case 1).—Gross appearance of the metastatic foci in several selected sections of the cerebrum (*A, B*) and cerebellum (*C*).

*Comment.*—In view of the immense destructive process in the cerebellum and the compression of the fourth ventricle by a tumor mass (fig. 1) and of the numerous metastatic nodules in the cerebrum, there would be little gained in attempts to correlate the anatomic observations with the clinical manifestations in the case. It will be sufficient to point out that the disseminated character of the objective neurologic signs pointed definitely to multiplicity of lesions, and that the early appearance of pronounced manifestations of increased intracranial ten-

sion is well explained by the location of a large metastatic mass about the anterior portion of the fourth ventricle which gave rise to an obstructive form of internal hydrocephalus. We have found in the course of this study that advanced bilateral papilledema, as in this instance, is found only when a metastatic focus is located somewhere in the posterior fossa or about the aqueduct of Sylvius, obstructing the normal flow of cerebrospinal fluid. Metastatic tumors in the cerebral hemispheres are less likely to cause and only rarely do cause changes in the optic disks.

The moderate cell count in the cerebrospinal fluid is in full accord with the experience that mild pleocytosis is not uncommon in metastatic tumors of the

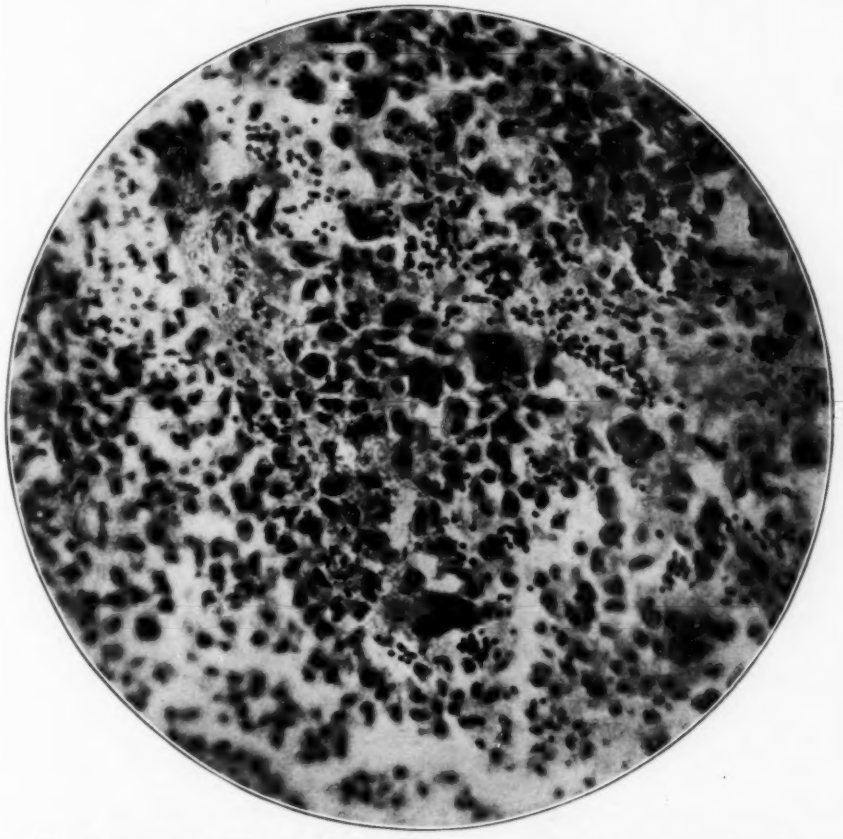

Fig. 2 (case 1).—Histologic appearance of a metastatic nodule. The "giant" cells with lobulated nuclei, which are probably in the process of amitotic division, should be noticed.

brain. The psychosis in this instance was a terminal event and cannot be regarded as specific for the pathologic process. The flaccid paralysis and the lost deep reflexes in the lower extremities suggest a similar metastatic involvement of the spinal cord and offer further support to the conception that a disseminated pathologic process, with an inflammatory lesion ruled out by the afebrile clinical course and negative serologic tests, can with a fair degree of safety be regarded as neoplastic and metastatic in character.

CASE 2.—*Cerebral manifestations of four weeks' duration.. Acute onset. Intense headache. Vertiginous attacks. Bruns' sign. Other signs of increased intracranial tension without papilledema. Dissemination of objective neurologic signs. Sudden death without operative intervention. Necropsy: Metastatic carcinoma.*

*Clinical History.*—J. Y., a man, aged 39, married, was admitted, Aug. 28, 1925, complaining of rapid loss of weight for the preceding four weeks, of intense headache and general weakness for three weeks, with attacks of vomiting for one week. The father of the patient died of cancer of the neck. Four weeks prior to admission, the patient noticed that he was losing weight rapidly and that his strength was declining. He complained of constant headache, with sharp shooting pain in the occiput. The headache and pain were frequently precipitated by sudden movements of the head. Of late, the headaches had become more intense and had been followed by frequent attacks of vomiting associated with vertiginous episodes. During such episodes he was disturbed by perceiving objects running before him from right to left; in response to them he would incline his body to the left. More recently the pain in the head became more intense and was associated with fainting spells lasting for several minutes.

*Examination.*—The patient was acutely ill and apparently in pain. He showed unequal pupils, the left larger than the right; increased left knee reflex, and a suggestive Babinski sign on the left There were no other signs; no abnormal masses were palpable, and no points of tenderness were noted.

*Course.*—On the day after admission, slight nystagmus to the left and bilateral ptosis were noted. A tendency toward a bilateral Kernig sign without rigidity of the neck appeared also. Lumbar puncture yielded clear fluid under normal pressure, with 15 cells per cubic millimeter. The serologic tests and analysis of the urine gave negative results. The temperature ranged from 98 to 99 F. No abnormal changes in the fundi were observed at any time.

Meningo-encephalitis was regarded as the most probable diagnosis, though it was thought that a cerebral neoplasm could not be ruled out entirely. The patient died suddenly without warning, eight days after admission.

*Necropsy Report.*—Gross Anatomy: The dura was normal. The pia-arachnoid was normal except for a small area on the dorsal surface of the left cerebellar lobe, where it was unusually smooth and glistening but thick and adherent to the underlying cortex. The brain was of average size and normal consistency except for the area on the dorsal surface of the left cerebellar lobe, underlying the thickened pia-arachnoid, where it was soft and fluctuating. On the under surface of the cerebellar hemisphere at the left pontofacial angle there was a small nodule, 1 cm. in diameter, which was hard and was easily shelled out (fig. 3). On section it had a granular appearance. A transverse midcerebellar section showed a similar, but somewhat larger mass, 2 cm. in diameter. It was also granular but much softer in make-up, particularly in its center.

Microscopic Anatomy: Section through the tumor mass in the cerebellum showed that the predominating type of cell was of the large squamous type, with considerable cytoplasm and large central nucleus. The cells were arranged in sheets surrounding large blood vessels. Numerous mitotic figures were seen, indicating rapid growth. Large areas of necrosis alternated with zones of rapidly proliferating cells. At the periphery of the tumor, the blood vessels showed dense perivascular infiltrations with small round cells, a condition often seen in neoplastic lesions of the brain, indicating a tissue reaction to the foreign (tumor) invader (fig. 4).

*Diagnosis.*—The condition was diagnosed as metastatic squamous-cell carcinoma.

*Comment.*—In this case, the diagnosis of meningo-encephalitis was in the foreground. The acute onset, the absence of decided localizing signs, and the presence of a slight rise in temperature and fifteen cells in the cerebrospinal fluid, indeed justified the assumption of an inflammatory lesion in preference to one of a neoplastic character. But, if one recalls that the striking features in the case were intense headache associated with sharp pain in the head and frequent attacks of nausea and vomiting, a scarcity of localizing signs and the rapidity

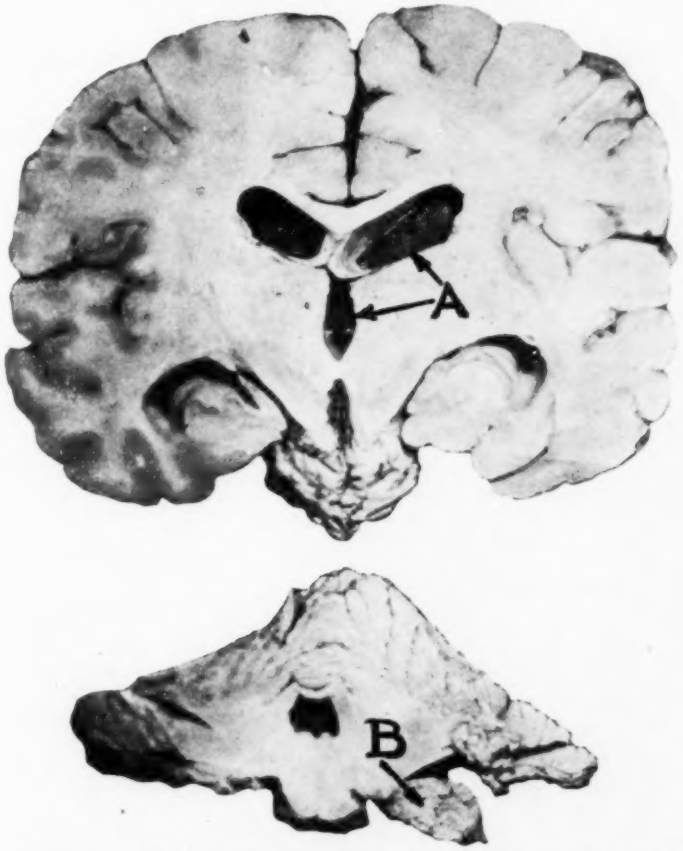


Fig. 3 (case 2).—Fairly advanced ventricular distention (*A*) and the small metastatic nodule in the pontofacial angle (*B*).

with which the clinical picture unfolded itself, he should find no difficulty in recognizing the neoplastic character of the lesion and its metastatic nature because of the disseminated features and the absence of changes in the disks.

It is striking that the cerebellum was singled out as the only seat for the metastatic tumor. This localization, however, fully explains the clinical picture, for it caused bilateral, symmetrical internal hydrocephalus. The latter, as is well known, may cause symptoms, which can simulate a diffuse inflammatory lesion of the brain as well as give rise to signs of meningeal irritation. The location of the tumor also will explain the Bruns' syndrome in the case. It is, however, difficult to account for the absence of changes in the disks.

CASE 3.—*Cerebral symptoms of three months' duration. Abrupt development of isolated, somewhat disseminated, neurologic signs. History of trauma. Sudden death without operation. Necropsy: Metastatic carcinomatous foci.*

*Clinical History.*—A. D., aged 46, a married woman, was admitted to the Mount Sinai Hospital, Feb. 26, 1923. The family and personal history presented no facts bearing on the present illness. The latter began about eight months prior to admission when it is said she accidentally (?) fell down a flight of stairs. The fall was attributed to darkness in the hall. She was badly shocked, but there were

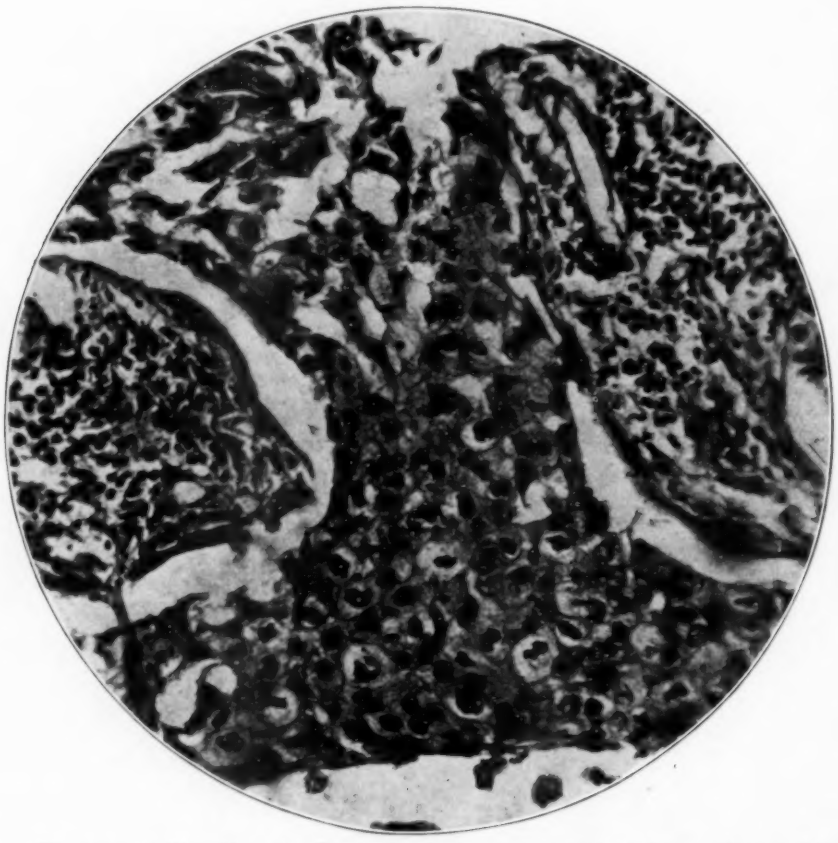

Fig. 4 (case 2).—The histologic appearance of a metastatic focus; the reactive infiltration, with small round cells about the blood vessels, a condition often seen in invasion of the brain by tumors, should be noted. It is not an inflammatory reaction in the accepted sense.

no loss of consciousness and no visible signs of injury. She recovered rapidly and remained well for a period of three months; she then suddenly developed marked speech disturbance which was ushered in by a convulsive seizure. At first there was gradual improvement in speech, but she soon began to complain of weakness in the right ankle. She consulted a physician who, because of the previous fall, considered the weakness of the ankle to be of local character and suggested baking and massage. The weakness at the ankle was soon followed by

more pronounced and widespread loss of power, gradually involving the entire right lower extremity. With extension of the paretic manifestations, speech once more became impaired. The patient began to stumble more frequently over words and phrases, and at times was unable to make herself understood. Shortly before admission to the hospital, she began to show mental signs characterized by dulling of intellect, confusion and impaired orientation. There was also complete loss of the power of speech.

*Examination.*—The patient was in a poor condition and showed marked general wasting. She was confused, disoriented and totally aphasic. The pupils were

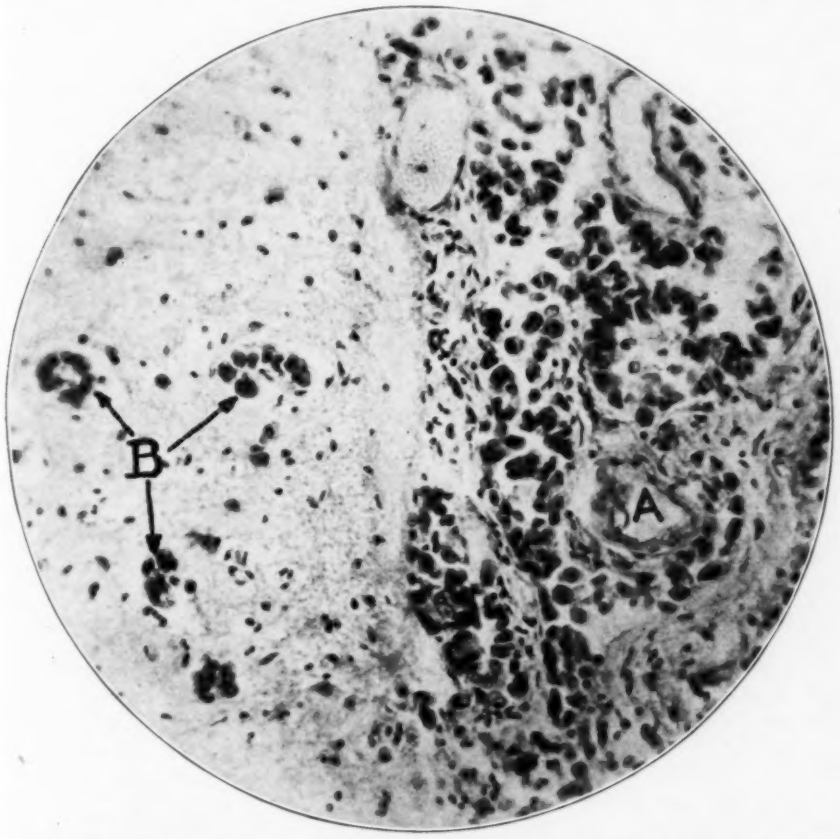


Fig. 5 (case 3).—Microscopic appearance of the neoplastic infiltration of the subarachnoid (*A*) and adventitial (*B*) spaces.

equal, regular, but sluggish to light and in accommodation. The eyegrounds were normal. There was no limitation of movements of the eyes. There was weakness of the left side of the face of the central type with right hemiparesis involving the arm and leg. There was general hyperreflexia with the deep reflexes more active on the right side. A Babinski sign and ankle clonus were present on that side. The cerebrospinal fluid and blood Wassermann tests were negative. In view of the history of trauma, traumatic meningo-encephalitis was the diagnosis considered.

*Course.*—The patient remained in the hospital for six days, declining rapidly and gradually passing into stupor, in which she died suddenly.

*Necropsy Report.*—Gross Anatomy: The dura showed no thickening, adhesions or hemorrhages anywhere. The pia-arachnoid was dull, particularly over the frontal lobe, with numerous small flattened areas, the size of a pinhead, scattered over the dorsolateral surfaces of the brain, particularly along the sulci in the course of the vessels. The gyri were flattened over the left frontal lobe in the region of the motor area. On incision, several areas were found, on the average from 3 to 5 mm. in diameter, each surrounded by a well organized and thickened capsule. They had the appearance of small metastatic "abscesses." These were found in the frontal lobe of the left hemisphere, in the precentral gyrus as well as the Broca's area. One nodule of this type was also found in the right frontal lobe.

Microscopic Anatomy: Sections taken at various points at which carcinomatous invasions were noted on gross inspection presented a uniform picture. Cancer cells formed collars about blood vessels consisting of one, two or more layers of cells; most frequently these cells were seen in the adventitial space of the blood vessels. Such cells were seen free in brain tissue only rarely, but even then, they were in proximity to a small vessel. The appearance of the meninges was most striking. The entire pia-arachnoid space was crowded with cancer cells which were mingled with other cellular elements such as gitter cells, lymphocytes and occasional fibroblasts. Here the cancer cells had a tendency also toward alveolar formation (fig. 5). The brain tissue in the vicinity of the carcinomatous nodules showed various changes such as edema, mild proliferation and neuronophagia.

*Diagnosis.*—The condition was diagnosed as metastatic carcinomas of the brain and meninges, primary in the sigmoid colon.

*Comment.*—The essential clinical features, though not unusual, are nevertheless significant in pointing the way to the right diagnosis. The sudden appearance in a patient, otherwise well, of an isolated neurologic manifestation such as drop-foot, followed in fairly rapid succession by the appearance of other isolated symptoms, such as aphasia, which undergo partial improvement before definite and more massive localizing signs and symptoms appear, should have been considered as an important diagnostic hint in favor of metastatic lesions of the brain.

A metastatic cerebral neoplasm becomes more than a probability in the absence of changes in the disks and when an afebrile course excludes an encephalitic process. Serologic examination must eliminate a syphilitic process and thorough examination of the ears and sinuses must be carried out to exclude a primary infectious focus so as definitely to eliminate abscess of the brain as a diagnostic possibility.

By consulting the anatomic description, one will find sufficient ground for almost all the clinical manifestations, local and general. The marked and diffuse meningeal infiltration and the few small nodules are to be considered as the important anatomic background for the terminal clinical picture.

CASE 4.—*Cerebral symptoms of six months' duration. Clinical picture clouded by presence of generalized arteriosclerosis and lack of decided evidence of increased intracranial tension. Amaurosis with terminal development of questionable changes in the disks and psychosis. Sudden death without operative intervention. Necropsy: Multiple metastatic carcinomas.*

*Clinical History.*—M. N., aged 68, married, a fruiterer, was admitted to the Mount Sinai Hospital, Dec. 15, 1923. He apparently had been well until the begin-

ning of the illness, which dated back six months. At that time he began to complain of short attacks of dizziness. Three months later, he noticed impairment of vision, though an ophthalmologic examination failed to reveal any apparent cause for the visual disturbance. More recently, he began to experience difficulty in swallowing

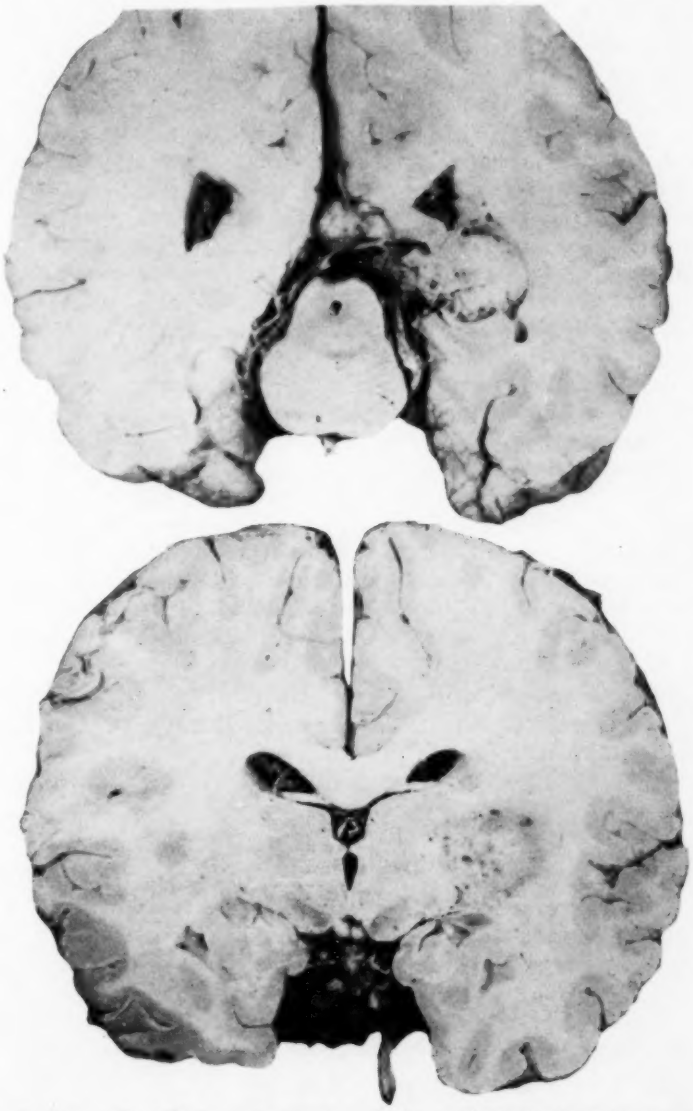

Fig. 6 (case 4).—Gross appearance of the metastatic foci in the cerebral hemispheres.

and developed general weakness and inability to sleep. A few days before admission, he commenced to suffer with left-sided headache, displayed weakness of the right arm and leg, and became completely blind. He soon became irrational, restless and resistive to care.

*Examination.*—The patient was brought to the hospital in poor condition, with signs of bilateral hypostatic pneumonia. He was somewhat delirious and showed bilateral neuroretinitis with slight elevation of the disks and paresis of the right arm and leg. The urine was normal; the blood count showed slight leukocytosis, and the blood pressure was 140 systolic, 110 diastolic.

*Course.*—The patient's condition declined rapidly, and he died five days after admission to the hospital.

*Necropsy Reports* (examination limited to the cranium).—Gross Anatomy: The meninges were normal. The brain showed evidence of increased intracranial pressure. In the left occipital lobe, 2 cm. anterior to the occipital pole, there was an area, about 3 cm. in diameter, which was invaded by a growth. This mass was wedge-shaped with its apex directed and inserted into the depth of the brain substance in which it was embedded. The opposite occipital lobe in the corresponding location was suspiciously flattened, and on incision presented a mass similar to the one described but more deeply located. The structures at the base of the brain, including the blood vessels, showed no pathologic changes. On incision, several other small metastatic masses were found. A small rounded mass about 1 cm. in diameter was seen on the level of the genu of the corpus callosum, invading the cortex in the middle and inferior frontal convolution, on the left side. Adjacent to this mass were two cystic cavities; the subcortex around and adjacent to the mass was edematous and swollen. Another mass was found in the subcortex on the left side adjacent to the corpus callosum just above the formation of the internal capsule, at a point at which the striatum was broken up into its constituent parts. Roughly on the level of the middle portion of the island, another large mass, about 2 cm. in diameter, was found in the subcortex, invading the internal capsule and partially involving the thalamus. On the level of the posterior third of the island of Reil, two small areas were found, larger on the left side than on the right and adjacent to the surface of the brain. The masses were brownish-red with a pinkish-white center (fig. 6).

Microscopic Anatomy: Section showed the tumor mass to be made up of alveoli lined by cuboidal and low columnar epithelium, some of the alveoli containing colloidal material.

*Diagnosis.*—The condition was diagnosed as metastatic adenocarcinoma, primary in the prostate.

*Comment.*—The question arose whether we were dealing with a vascular or neoplastic lesion and, in view of the ophthalmologist's report that the fundi presented a picture of neuroretinitis arteriosclerotica with hemorrhages, the case was regarded as an instance of cerebral arteriosclerosis with areas of softening. However, the rapidity with which the neurologic picture was unfolding and the marked dissemination of fairly circumscribed lesions in the face of a rather moderate blood pressure led one to suspect multiplicity of lesions in the nature of multiple neoplasms, though their metastatic character was not recognized.

The gross anatomic picture provides ample explanation for the general as well as the isolated clinical features. The bilateral involvement of the optic tracts may be considered as the cause of the amaurosis. The proximity of a large mass to and compressing the third ventricle resulted in moderate ventricular distention. The diffuse and extensive degenerative changes with edema of the tissue of the brain adjacent to the many neoplastic foci probably were responsible for the terminal psychotic manifestation.

GROUP 2

CASE 5.—*Cerebral manifestations of four weeks' duration. Headache, vomiting and Bruns' symptom. No papilledema. Terminal development of disseminated cerebral signs and evidence of meningeal involvement. Rapid decline, death and necropsy. Metastatic carcinomas with a nodule in the fourth ventricle.*

*Clinical History.*—T. B., a housekeeper, aged 52, divorced, was admitted, March 31, 1923, with the complaint of headache and vomiting of four weeks' duration. She had had influenza four years previously and had passed through the menopause two years previously. The present illness, acute in onset, was attributed to overindulgence in food. It began with severe headache, vomiting and pain in the abdomen. The headache became constant and increased in severity. It was limited chiefly to the left frontoparietal region. The epigastric pain became less constant. The vomiting, which was not related to meals, continued; it was usually preceded by a great deal of retching and was frequently precipitated by sudden movement of the head or of the body. The vomitus contained occult blood.

*Examination.*—The patient was poorly nourished and presented an appearance of chronic illness. She had an acetone breath and was somewhat drowsy. There were rigidity of the neck, bilateral Kernig and Brudzinski signs, and bilateral blurring of the nasal halves of the disks. The latter was considered by the ophthalmologist as incipient papilledema. The pupils were equal and reacted to light promptly. There were right hemiparesis with increased deep reflexes, absence of the abdominal reflexes and a positive Babinski sign on the same side. There was incontinence of urine and feces. Lumbar puncture yielded clear fluid under increased pressure, with 100 lymphocytes. The blood and spinal fluid Wassermann tests were negative; the colloidal gold curve in the spinal fluid was also negative. The blood chemical determinations gave normal figures. A blood count showed 5,600,000 red blood cells, and 11,000 white cells, with 80 per cent polymorphonuclear leukocytes. The blood pressure was 120 systolic, 90 diastolic.

*Course.*—The first week in the hospital was marked by the development of mild hypalgesia and slight ptosis on the right side and reduction in the pupillary reaction to light. The case was considered one of epidemic meningo-encephalitis while a cerebral neoplasm was regarded only as a remote possibility. Soon, however, additional symptoms appeared, such as paralysis of upward gaze, weakness of the right internal rectus muscle with poor convergence, and tenderness on percussion over the left side of the skull. The diagnosis of meningo-encephalitis was still regarded as most probable. A cell count in a second lumbar puncture showed 128 lymphocytes.

On April 17, more definite evidence of involvement of the third nerve appeared: ptosis of the right upper eyelid, fixation of the pupil on the right side, and general paralysis of the internal and superior recti. The papilledema became more marked and examination of the larynx showed paralysis of the left abductor. Gastric analysis showed absence of free hydrochloric acid and total acid of 30. In view of the gastric observations and the increasing papilledema, the possibility of metastatic neoplasm came under consideration. Another lumbar puncture yielded 60 lymphocytes per cubic millimeter.

Throughout the residence in the hospital, the patient declined rapidly, vomited repeatedly and grew progressively weaker. She died on the twenty-fifth day in the hospital.

*Necropsy Report.*—Gross Anatomy: The meninges were smooth and glistening and showed no exudate or hemorrhages. There was no decided evidence

of increased intracranial pressure. On section of the brain, a few small yellowish areas were found scattered through the left frontal lobe, measuring about 1 cm. in diameter. They were sharply demarcated from the surrounding brain tissue. The ventricles appeared dilated. Sections of the cerebellum showed a mass, 2 by 3 cm., of yellowish-brown tissue in the substance of the right lateral lobe. In the fourth ventricle was a small pedunculated spherical tumor springing by a narrow pedicle from the floor of the ventricle. The tumor measured about 1.5 cm. in all directions (fig. 7).

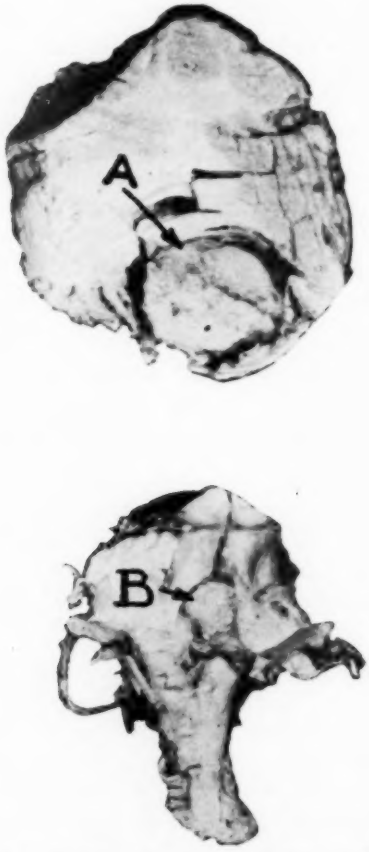


Fig. 7 (case 5).—Gross appearance of several of the metastatic nodules (*A, B*); the small mass on the floor of the fourth ventricle (*B*) is plainly visible.

Microscopic Anatomy: Sections from the cerebellum, from the mass in the floor of the fourth ventricle, and from the pituitary body showed the growth to be metastatic nodules of a tumor that was primary in the lung. The histologic character of the tumor was identical with that of the primary growth. It was made up of numerous alveoli, lined by tall cuboidal epithelium and filled with mucous secretion (fig. 8).

*Diagnosis.*—The condition was diagnosed as multiple metastatic carcinoma, primary in the bronchus.

*Comment.*—The precipitate onset, the disseminated organic characteristics, the meningeal signs and the pleocytosis justified to some extent the diagnosis of meningo-encephalitis. However, the intense headache, the Bruns' syndrome, the tenderness to percussion and the suggestive gastric analysis should be regarded as of sufficient weight to decide in favor of a diagnosis of metastatic tumor of the brain. What is there in the gross anatomic changes to justify some of the essential clinical manifestations? The outstanding neurologic sign—the Bruns syndrome—found its anatomic basis in the presence of a small nodule in the fourth

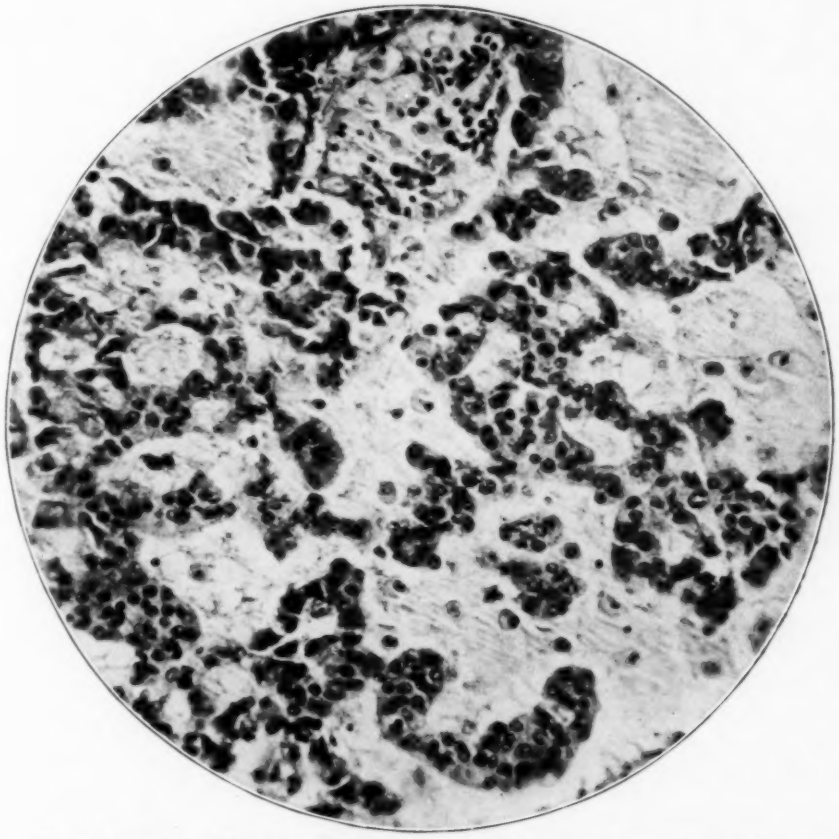

Fig. 8 (case 5).—The microscopic structure of the tumor mass in case 5, showing the alveolar arrangement of the cellular elements.

ventricle. The dissemination of the physical signs was parallel to similar dissemination of anatomic lesions. The pleocytosis was due to the proximity of the neoplastic nodules to the overlying ependymal lining.

Case 6.—*Cerebral symptoms of six months' duration. History of pulmonary involvement for five years. Disseminated neurologic signs. Meningeal involvement. Terminal psychosis. Rapid decline. Death without operation. Necropsy: Metastatic carcinomatosis of the brain and meninges.*

*Clinical History.*—F. M., a salesman, aged 44, married, was admitted to the Mount Sinai Hospital, Oct. 13, 1924, complaining of noises in the head and ears

for the last six months; hoarseness for the last eight weeks; pain between the shoulders, severe occipital headache and dizziness for the last two weeks. In the past history the only facts of importance are: occasional attacks of dyspnea on slight exertion, weakness and palpitation for five years associated with mild but persistent cough without hemoptysis or night sweats. The present illness began, six months prior to admission to the hospital, by the appearance of an annoying noise in the head and ears and the development of general malaise. The patient began to lose weight. Four months later he suddenly became hoarse. Five weeks later, vision became impaired. More recently he began to experience severe, knife-like pain between the shoulder blades and severe occipital headache accompanied by attacks of dizziness. Lumber puncture at that time relieved the headache.

*Examination.*—The patient was in a poor condition with marked wasting and an involvement of the lung, moist râles being present all over the chest. The pupils were irregular and unequal, the left fixed to light, ptosis of the right eyelid, left facial weakness and slight paresis of the arm. The upper deep reflexes were active and equal; the knee reflexes, which had been elicited several days previously, were absent and the abdominal reflexes were diminished. Laryngoscopic examination revealed slight impairment of motion of the left side of the palate and a cadaveric position of the right vocal cord. The ophthalmologist reported normal fundi, and the otologist discovered mixed deafness on the right and total deafness on the left side. Roentgen-ray examination of the chest was reported as normal.[3] Wassermann tests with the blood and spinal fluid were negative. The colloidal gold test of the spinal fluid gave a paralytic curve. The urine was normal. No abnormal masses or tender areas were noted in the abdominal or thoracic cavities.

*Course.*—Among the diagnostic possibilities considered was meningo-encephalitis, tuberculous or syphilitic in nature. The final clinical diagnosis, however, was a diffuse neoplastic process of the meninges of the brain and spinal cord. The short stay in the hospital was marked by rapid decline. The meningeal symptoms became more prominent; rigidity of the neck and Kernig signs increased, and complete areflexia developed. The patient then displayed psychotic manifestations, became dyspneic and died on the tenth day of his residence in the hospital.

*Necropsy Report.*—Gross Anatomy: The dura was somewhat adherent to the skull, especially in the midline. The pacchionian bodies were prominent. The pia-archnoid was slightly congested. The left optic nerve showed a bulbous swelling extending from a point a little above the optic tract, which appeared to be invaded by a tumor mass; this was a deep gray and its consistency was firmer than that of the right nerve. It was from 5 to 6 mm. in diameter. On the surface of the meninges, a short distance to the left of the mass, was another tumor mass, a small, grayish-white, pearly, firm papule, about 2 mm. in diameter. No evidence of tumor could be found anywhere else over the surface of the brain or along any of the other cranial nerves.

The spinal cord showed a bulbous enlargement corresponding to the region of the first lumbar segment. This swelling was just above the normal enlargement corresponding to the region of the ninth and twelfth dorsal segments. Externally, this portion of the cord was of normal color, but slightly firmer in consistency. The meninges covering the spinal cord showed no gross pathologic changes. The spinal nerves likewise were all grossly normal.

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3. A later study of the roentgenograms showed definite neoplastic involvement of the lung.

Microscopic Anatomy: Sections of the cerebral cortex with its meningeal coverings, the brain stem, the left optic nerve (fig. 9), and the spinal cord showed diffuse metastatic infiltration of the meninges and, in isolated areas, of the brain substance with a malignant neoplasm, which was primary in the lung. The histologic appearance was that of an adenocarcinoma and was similar to that of the primary mass in the bronchus.

*Comment.*—The early appearance of tinnitus and the later development of partial aphonia served as evidence of peripheral involvement of the eighth

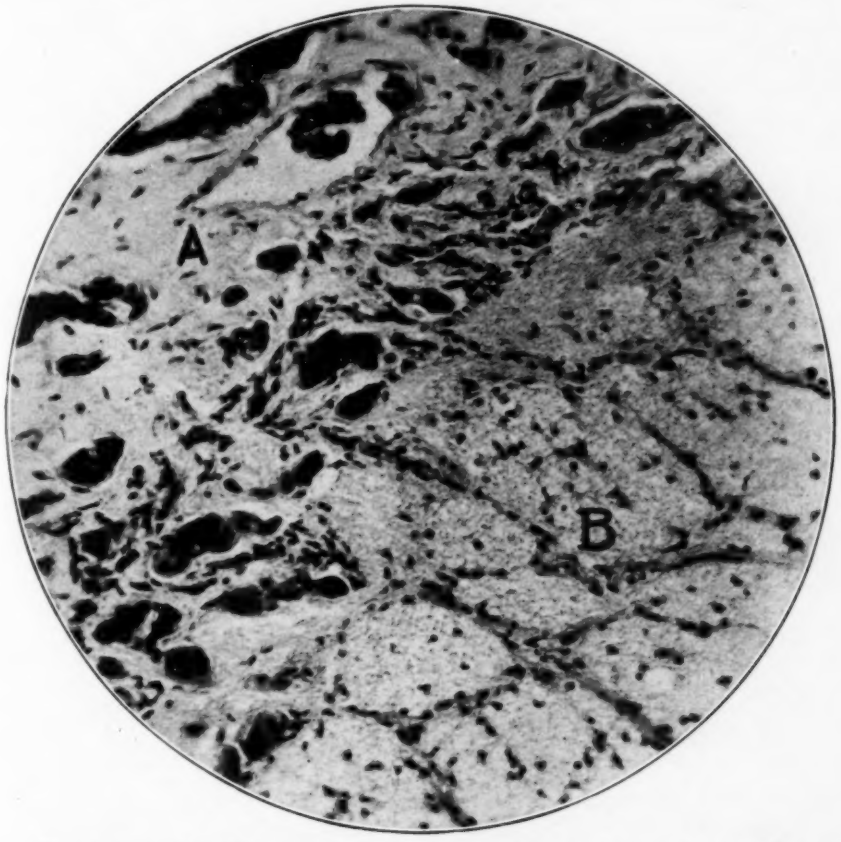


Fig. 9 (case 6).—Microscopic appearance of the tumor mass (*A*) infiltrating the optic nerve (*B*).

and tenth cranial nerves. The appearance of meningeal manifestations—the radicular pain in the upper dorsal region and the loss of deep reflexes in the lower extremities—accompanied by symptoms of increased intracranial tension, such as headache and dizziness, added to the infranuclear pareses of the cranial nerves and pointed strongly in the direction of a diffuse meningeal process, disseminated in character, involving the brain and spinal cord. The addition of other paretic phenomena, central in type, such as the paresis of the right arm, indicated that the process extended into the brain substance, giving rise to an encephalomeningeal condition.

The causative agent remained for a time undetermined. A tuberculous process was considered but was excluded by the repeated failure to find the causative organism; the negative Wassermann tests in the blood and spinal fluid showed that syphilis was not the causative agent. Thus a neoplastic process involving diffusely the meninges and adjacent brain structures was regarded as the most probable pathologic process. This was supported by the initial slowness with which the clinical picture developed, by the gradual, step-by-step involvement of the cranial nerves and the terminal appearance of a psychic disturbance, which is not uncommon in carcinomatous meningitis.

The anatomic observations fully explain the clinical manifestations and require no further comment. However, the histologic picture is significant, indicating a much greater neoplastic involvement of the meninges than the gross appearance of the brain and its coverings would suggest. The resemblance between this case and case 1 is striking. In both instances radicular pain, indicating meningeal involvement, was an initial occurrence in the clinical course.

GROUP 3

CASE 7.—*Cerebral manifestations of three weeks' duration. Sudden onset. Disseminate neurologic signs with evidence of increased intracranial pressure. History of previous removal of malignant tumor of the leg. Sudden death without operative intervention. Necropsy: Metastatic melanoblastoma of the lateral ventricle.*

*Clinical History.*—B. G., aged 21, an actress, was admitted to the Mount Sinai Hospital, April 14, 1919. She had had measles and mumps in infancy. Three years before admission, a pigmented mole was removed from the leg, which was diagnosed as a melanosarcoma; three weeks later the inguinal glands became enlarged. They were found to be infiltrated and were excised. There was no further recurrence. Five weeks before admission, the patient had bronchitis and made an uneventful recovery. Three weeks before admission, she suddenly had an attack of vomiting and became stuporous. This episode was attributed to an indiscretion in diet and there was only a slight rise in temperature. She remained in the stupor for two days. She then recovered sufficiently to be up for about ten days. During that time she felt somewhat drowsy, complained of headache, pain behind the eyes, inability to look at a bright light and occasionally of double vision. During the nine days before admission, the headache became more intense; she vomited frequently and gradually became confused, with a slight rise in temperature.

*Examination.*—This revealed equal, regular pupils which reacted to light and in accommodation; bilateral ptosis, greater on the left than on the right; weakness of the left external and internal recti, and bilateral papilledema with 3 diopters elevation and retinal hemorrhages and exudates. The tongue deviated to the right, and bilateral facial weakness, more marked on the left, was present. The deep reflexes of the upper extremities were diminished but equal; the knee reflexes could not be elicited; the Achilles reflexes were lively and equal. No pathologic reflexes were obtained. The patient was somewhat disorriented and euphoric.

The blood Wassermann test and the roentgen-ray examination of the skull gave negative results. Lumbar puncture yielded xanthrochromic fluid under increased pressure with 8 cells per cubic millimeter. The blood pressure was 110 systolic and 77 diastolic. The blood count was within normal limits.

*Course.*—The diagnosis at this time rested between metastatic tumor and acute epidemic encephalitis. There appeared at first a suggestion of improvement; the drowsiness disappeared and the diplopia became less marked, which strengthened the belief that the case was one of encephalitis. Shortly thereafter, however, another decline, with the appearance of additional objective signs, occurred. These were exophthalmus on the right, jerky movements of both hands, more marked on the left side, weakness of the right grip, and disjointed independent movement of both eyes. At this time, it was generally agreed that the condition was caused by tumor, and operation was seriously considered, although it was still difficult to localize the lesion. Another lumbar puncture at this time again showed xanthochromic fluid.

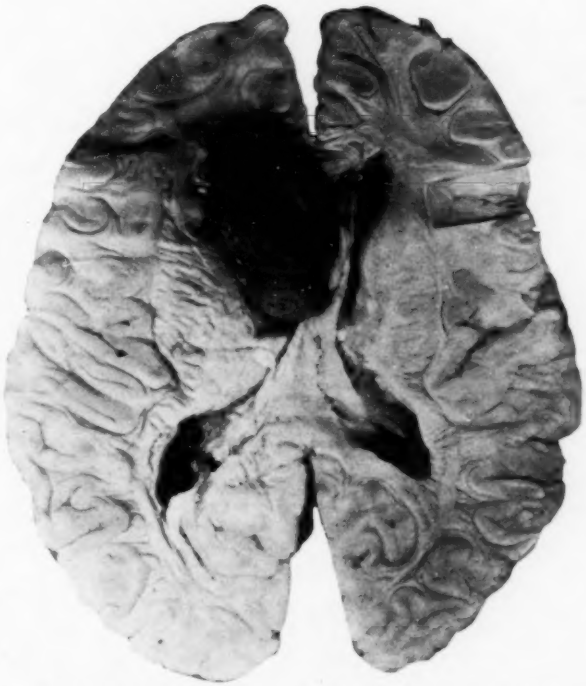

Fig. 10 (case 7).—Gross appearance of the single, pigmented tumor (melanoblastoma). The discrete demarcation and the limitation to a portion of the left lateral ventricle should be noted.

Following another slight remission, there was a rapid decline, death occurring suddenly after the patient had swallowed a small amount of strong ammonia by mistake.

*Necropsy Report.*—(Examination limited to the cranium.) Gross Anatomy: The brain showed slight flattening of the convolutions. On section, a large mass, not unlike a clot of blood, was found in the body of the left lateral ventricle. This red mass was about the size of a hen's egg and showed evidence of organization (fig. 10). The foramen of Monro was closed on this side. The walls of the ventricle showed dark pigmentation. In the centrum semiovale on the same side was an area of discoloration. This discoloration also had affected the thalamus and the caudate nucleus on the same side. The remainder of the

ventricle on this side was apparently dilated. There was a small area suggesting a subcortical hemorrhage, about the size of a pea, in the posterior end of the second temporal convolution. No evidence of neoplasm was seen. The vessels at the base of the brain were extremely small and thin-walled for a woman of the patient's age.

Microscopic Anatomy: Histologic study of the so-called blood clot in the ventricle disclosed a tumor, its structure being that of a melanoblastoma (fig. 11).

*Diagnosis.*—The condition was diagnosed as metastatic melanoblastoma.

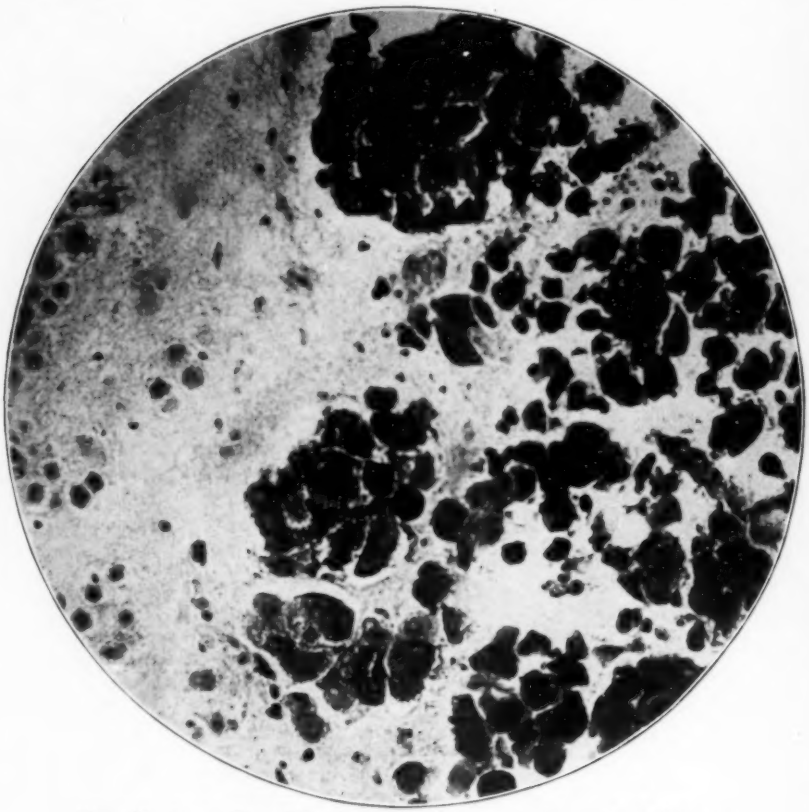

Fig. 11 (case 7).—Histologic structure of the melanoblastoma.

*Comment.*—The occurrence during an epidemic of acute encephalitis of an illness characterized by the acute onset, striking irregularity in the clinical course and the disseminated character of the objective manifestations, coupled with periods of lethargy, justified the suspicion of an inflammation. Despite this, a metastatic neoplasm was seriously considered; the clinical picture, in view of the history of previous removal of a malignant neoplasm, left little doubt that this was metastatic tumor of the brain.

It is interesting to note that in this case, which was for some time considered one of acute epidemic encephalitis, the original anatomic diagnosis was also encephalitis with intraventricular hemorrhage, because the intraventricular mass appeared so much like a hemorrhage and so unlike a tumor. Six years elapsed

before more thorough study led to the discovery that the so-called organized hematoma was a metastatic melanoblastoma. The position of the tumor fully explains the frequent oscillations in the clinical picture; it also explains the marked internal hydrocephalus with resultant papilledema and xanthochromic fluid, and the stormy character of the clinical course. Worthy of note also is the fact that the tumor was one single, large metastatic mass.

CASE 8.—*Cerebral manifestations of one month's duration. History of previous removal of malignant neoplasm of the toe. Acute onset of signs of focal cerebral involvement without decided signs of increased intracranial tension. Sudden death without operative intervention. Necropsy: Metastatic melanoblastoma of the brain.*

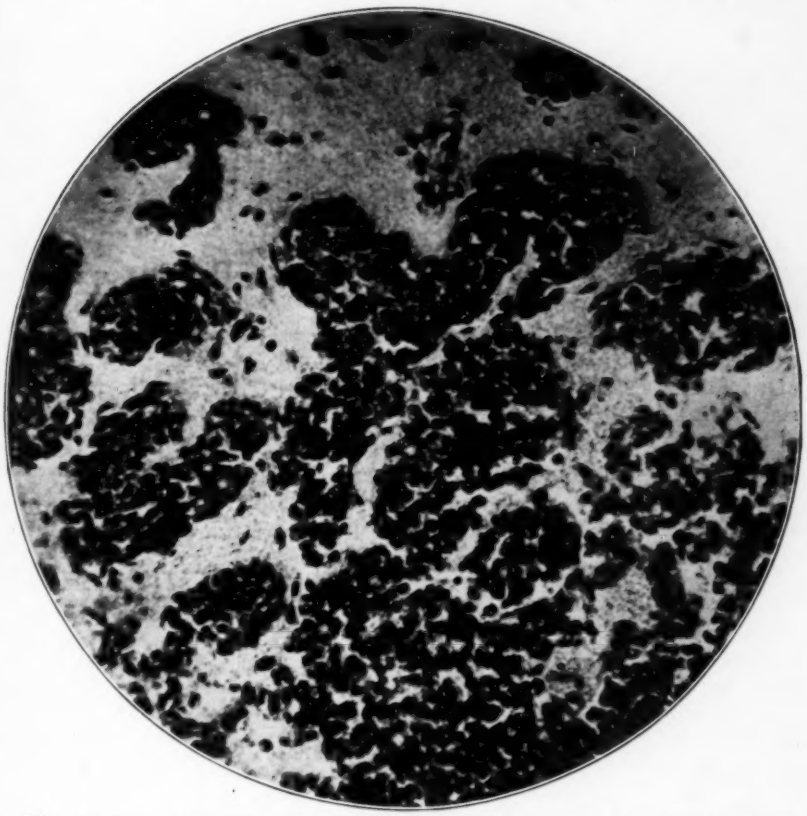

Fig. 12 (case 8).—Microscopic appearance of the tumor (melanoblastoma); compare with figure 11.

*Clinical History.*—B. M., a housewife, aged 37, married, was admitted to the Mount Sinai Hospital, Nov. 19, 1925. Two years before she had been admitted to the hospital, and a toe had been amputated for a darkened pigmented area, which was considered an early stage of a melanocarcinoma and later was reported by the pathologist as such. The patient remained well until one month before the second admission when she complained of urinary incontinence and occasional

attacks of nausea. She also began to experience difficulty in speaking. Two weeks later, during the night, she suddenly lost consciousness for a period of ten minutes and, on arising the next morning, noticed weakness in the right arm and leg.

*Examination.*—The patient presented a right hemiparesis involving the face, arm and leg, with signs of involvement of the pyramidal tract, such as increased deep reflexes, diminished abdominal reflexes and a positive Babinski sign on the right side. The left pupil was slightly larger than the right; both pupils reacted well to light and in accommodation. There were no papilledema or ocular paralyses. The blood and cerebrospinal fluid Wassermann tests were negative. Examination of the chest disclosed a loud bruit, not unlike that heard in aneurysms, over the right infraclavicular region. The pulses, however, were equal and synchronous. Examination of the abdomen revealed no masses or tender areas.

A roentgenogram of the chest disclosed a number of circular areas, apparently metastatic masses, in the left lung. With this in mind, and in view of the history of amputation of the toe, the diagnosis of metastatic melanocarcinoma of the brain was made and the case considered inoperable.

*Course.*—The patient's residence in the hospital was marked by progressive decline. Later in the course, several jacksonian seizures involving the right side occurred. The disks developed mild swelling. Finally, on December 11, the patient had a generalized convulsion which terminated in death.

*Necropsy Report.*—Removal of tissue was possible only through a small trephine opening. A small scalpel was passed through the wound in the direction of the left frontal precentral region, and tumor tissue was brought out in large masses. It was dark brown, granular and friable. The histologic picture was that of a melanocarcinoma (fig. 12).

*Comment.*—In this case also the signs and symptoms of cerebral involvement appeared acutely. The clinical course was extremely rapid, and the symptoms of involvement of the nervous system occurred without changes in the disks, evidence of marked intracranial pressure, rise in temperature and evidence of syphilitic infection. They pointed strongly in the direction of metastatic neoplasm of the brain.

The postmortem study in this case was too meager to permit a full discussion of the relationship of the gross anatomic changes to the various physical characteristics. The latter, however, pointed to a well circumscribed lesion in the left cerebral hemisphere, and in view of the fact that in the other two cases of metastatic melanoblastomas (cases 7 and 9) the metastatic lesions were single, it would appear probable that here, also, there was only one single metastatic focus.

CASE 9.—*Cerebral symptoms of four weeks' duration. History of previous removal of malignant tumor of the face. Acute onset of signs and symptoms of increased intracranial tension. Initial symptom—severe headache. Disseminated objective characteristics. Rapid decline. Death without operative intervention. Necropsy: Metastatic melanocarcinoma.*

*Clinical History.*—L. J., an engraver, aged 29, married, was admitted to the Mount Sinai Hospital, June 14, 1924, complaining of headache and dizziness. The family history was unimportant. Two years previous to the onset of the present illness, a tumor was removed from the cheek which at that time was considered to be a squamous cell carcinoma. The patient remained well up to four months prior to admission to the hospital, when he began to suffer with bitemporal headache and attacks of dizziness. He was forced to give up work

because of the constant headache, dizziness and the gradual development of impairment of vision. More recently, diplopia and attacks of vomiting developed.

*Examination.*—On admission, the patient was in good physical condition, with the following positive objective neurologic characteristics: unequal pupils, the right larger than the left, and both reacting normally to light and in accommodation; bilateral rotary nystagmus; bilateral exophthalmos; bilateral corneal hyper-

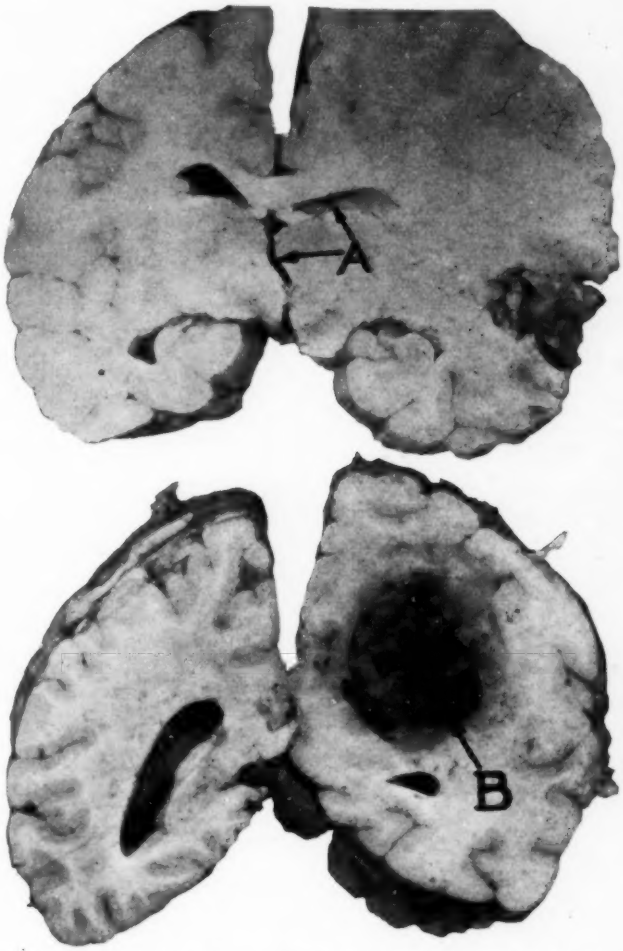


Fig. 13 (case 9).—Gross appearance of the tumor mass (*B*) (melanoblastoma). The distortion and compression of the third ventricle (*A*) should be noted.

esthesia; bilateral papilledema; tendency to left homonymous hemianopia; bilateral external rectus weakness; bilateral facial paresis, more marked on the right side; weakness of muscles of mastication on the right side. Serologic study of the urine, blood chemical determinations, blood and spinal fluid showed them all to be normal; twice repeated roentgenography of the skull failed to reveal any abnormality. Examination of the thoracic and abdominal organs revealed no abnormalities.

*Diagnosis.*—The diagnosis considered at this time was cerebral neoplasm, most likely suprasellar in location. In view of the history of previous removal of a malignant tumor, a metastasis was suspected.

*Course.*—The stay in the hospital was marked by progressive decline in the general condition and by advancing papilledema. In an attempt to save the sight, bilateral subtemporal decompression was performed, but this did not interrupt the steady decline, death occurring about five weeks after admission to the hospital.

*Necropsy Report.*—(Examination limited to the cranium.) Gross Anatomy: In the right occipital region a discolored area was noted, in the center of which was a small opening through which yellowish clear fluid was slowly exuding. When an incision was made at this level a large neoplastic mass was found, nodular in structure, granular in appearance and varying from pearly-white in some areas to brownish-red in others (fig. 13).

Microscopic anatomy: Brain. A section through the most typical portion of the neoplasm presented a fairly uniform picture, strikingly like that in case 8. Cells of three varieties were seen: (1) Those epitheloid in character and polygonal in shape, containing large, round, vesicular nuclei. These cells were grouped around blood vessels, giving the impression of an arrangement seen in perithelioma, and presented a nest-like appearance. (2) A cell, fusiform in outline, forming bands encircling the nests described above. (3) A bladder-shaped cell with small pyknic nucleus, filled with a coarse, brown pigment. Numerous mitotic figures were seen everywhere, and large hemorrhagic areas were encountered.

*Diagnosis.*—The condition was diagnosed as metastatic melanosarcoma.

*Comment.*—Attention is drawn to the following facts in the clinical history: the acute onset of headache and dizziness with the development of neurologic objective signs pointing to a disseminated lesion. The fixed facies and the diplopia, due to bilateral external rectus weakness, could be considered as encephalitic, if it had not been for the hemianopia and bilateral papilledema, signs that warned of a focalized neoplastic lesion. The history of a primary lesion elsewhere made the metastatic character of the lesion probable.

Little difficulty is found in correlating the anatomic observations with the clinical manifestations. This is particularly true of the left homonymous hemianopia with the tumor mass almost completely replacing the right occipital lobe. The bilaterality of some of the signs suggested at one time a suprasellar localization, but a neoplasm of the type and location described will compress the third ventricle and thus give rise to internal hydrocephalus, which in turn results in bilaterality of neurologic signs and in papilledema. Here again it is striking that the metastatic process was a single mass.

GROUP 4

CASE 10.—*Cerebral manifestations of seven weeks' duration. Acute onset. Diagnosis of tumor in the left frontal region. Craniotomy. No tumor recognized. Necropsy: Metastatic carcinoma (single) in the left superior parietal lobule.*

*Clinical History.*—W. E., a clerk, aged 46, married, was admitted to the Mount Sinai Hospital, March 25, 1917. For seven weeks, he had experienced difficulty in speech. The illness began, December 15, when the patient suddenly had an attack of vertigo. Somewhat later, the speech was noticed to become thick; on January 1, two weeks after the first attack, he had a second episode of dizziness, with loss of consciousness. On January 25, another attack took place, which was characterized by vomiting, dizziness and temporary loss of consciousness. Soon

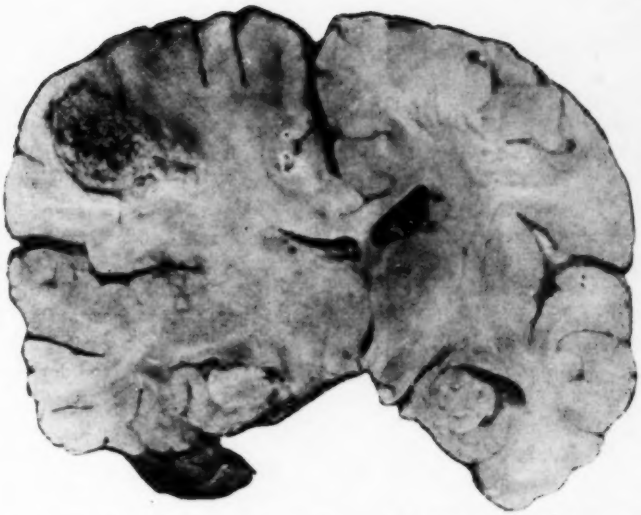

Fig. 14 (case 10).—Gross appearance of the single metastatic nodule. The compression of the lateral ventricle on the ipsilateral side and the displacement of the third ventricle should be noted.

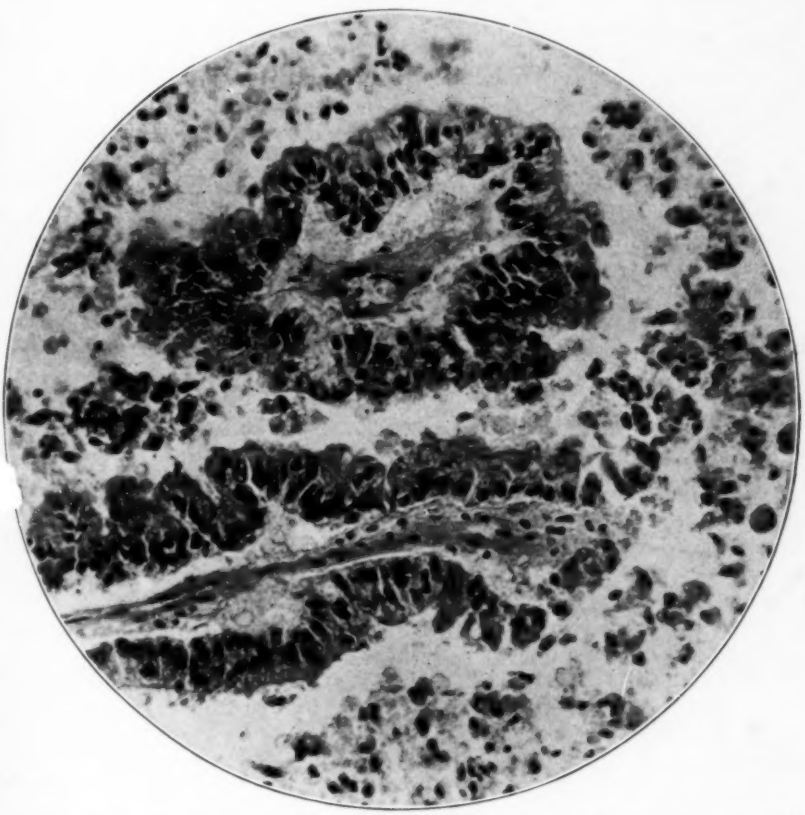

Fig. 15 (case 10).—Histologic appearance of the tumor; compare with figure 14.

after, frequent attacks of headache and mild hemiparesis with paresthesias on the right side developed; the vomiting became projectile in character and more frequent; still more recently, the patient became unable to read or write; speech was markedly impaired and the mentality dulled.

*Examination.*—On admission the patient showed: dulness and apathy; motor aphasia; bilateral external rectus weakness; bilateral papilledema of moderate degree; hemiparesis; hyperreflexia and a Babinski sign on the right side; mild bilateral Kernig sign and slight retraction of the neck; definite tenderness on percussion over the left frontal region. A roentgen-ray examination of the skull showed slight enlargement of the sella turcica with absorption of the anterior and posterior clinoid processes. Tests of the cerebrospinal fluid, blood and urine were all negative.

*Course.*—A cerebral neoplasm in the left frontal region was diagnosed, and on March 17, an exploratory craniotomy with right subtemporal decompression was carried out. No tumor was found; the patient's condition declined rapidly; terminal pulmonary edema set in, and the patient died on April 3.

*Necropsy Report.*—(Examination limited to the cranium.) Gross Anatomy: The left cerebral hemisphere was decidedly larger than the right; the enlargement was most marked in the region of the parietal lobe. The left hemisphere in this region measured 8 cm. from the sagittal fissure outward to the periphery, at the level of the posterior commissure. The right hemisphere measured 6.5 cm. There was enlargement of the left hemisphere dorsoventrally in the same section. The convolutions of the left hemisphere were much flattened, especially in the region of the superior parietal lobule. The fissures in the same region were shallow. The bulging of the parietal lobe was especially well marked in the region of the interparietal fissure, at its intersection with the postcentral fissure. A section of the brain showed that the bodies of the lateral ventricles were only slightly dilated. The corpus callosum was dislocated to the right, about 1 cm. beyond the midline. The neoplasm was about 4 cm. in diameter and lay beneath the cortex, almost entirely within the area of the superior parietal lobule. It was surrounded by an area of softening, varying in thickness from 1 to 2 cm., which demarcated the tumor from the surrounding brain substance. There was only a thin layer of cortex overlying the tumor, which was undisturbed (fig. 14).

The hypophysis was about twice the normal size but appeared grossly normal. When it was removed, the sella turcica had an eroded, dark appearance.

Microscopic Examination: Tumor. Sections of the tumor had the appearance of a metastatic carcinoma (fig. 15).

*Diagnosis.*—The condition was diagnosed as metastatic carcinoma.

*Comment.*—This is one of the uncommon instances of metastatic neoplasm which, because of well localized signs in the presence of evidence of increased intracranial pressure, had to be interpreted in terms of a focal, probably primary, neoplasm of the brain However, the acuteness of the onset and the rapidity with which the symptoms, signs and gravity of the clinical picture developed should have led to the suspicion of the malignant character of the neoplasm.

Of interest also in this case is the singularity of a metastatic lesion, as these lesions usually are multiple. Single lesions were observed also in two of the three cases of melanoblastomas, and in the third this was suspected. This feature permits the suggestion that operative intervention, even in suspected metastatic neoplasms, is not contraindicated, for the mass, though metastatic, may be single and removable; on the other hand, little is lost if the lesion proves to be multiple.

CASE 11.—*Cerebral manifestations of three months' duration. Acute onset with symptoms of increased intracranial tension. Later, signs of meningeal irritation. Diagnosis of tumor in posterior fossa. Suboccipital exploration. Malignant character of tumor recognized. Rapid decline. Death after second partial removal of tumor tissue. Necropsy: Metastatic multiple sarcomas.*

*Clinical History.*—B. G., a schoolboy, aged 10, who, aside from having had diphtheria at the age of 7 and measles at the age of 9, had always been well, was admitted to the Mount Sinai Hospital, Aug. 4, 1923, complaining of headache, vomiting and double vision. The onset was sudden, about three months prior to admission, when one morning he suddenly began to vomit. The attacks of vomiting recurred from every three to seven days. A month later, headache developed which was at first generalized, but later became localized to the right frontal region. The general numbness of which the patient complained at the onset of his illness had now become localized to the left half of the body. During the last two months, he had also experienced double vision, and more recently he had developed a buzzing sensation in the left ear and shooting pain in the left leg.

*Examination.*—On admission, the boy was poorly developed and anemic. He was somewhat drowsy and apathetic, and constantly complained of pain in the right temporal region. Tenderness on percussion was elicited over that region. There were: bilateral papilledema with temporal contraction of both visual fields; bilateral ptosis; left externus rectus weakness; horizontal nystagmus to the left; deviation of the tongue to the left; left hemiparesis with slight tremor of the left hand; increased left knee and ankle reflexes; diminished left abdominal reflexes and absent left cremasteric reflex. No Babinski sign was elicited. There were also left hemihypesthesia and hemihypalgesia, slight rigidity of the neck and slight bilateral Kernig sign. A positive Weber sign was elicited on the right. Examinations of the blood, spinal fluid and urine yielded negative results.

*Course.*—The diagnostic possibilities considered at the time of admission were: neoplasm in the brain stem blocking the interventricular communication, or an ependymoma in the aqueduct of Sylvius. The marked papilledema indicated a neoplasm in the posterior fossa, and operative intervention was considered urgent.

Suboccipital craniotomy was performed in two stages. In the right cerebellar lobe, two grayish masses were noticed beneath the pia-arachnoid. In the opinion of the surgeon, they appeared not to have involved the brain tissue proper. The nodules had a lymphoid appearance and were believed to be metastatic sarcomas with the primary lesion elsewhere.

The operation was at first followed by improvement in the general condition, though the neurologic status remained unchanged. The patient was allowed to go home. Ten days later, on August 2, he again began to complain of severe headache; he began to vomit frequently, became aphasic and lost power in the limbs. He gradually passed into stupor, and in this condition was readmitted to the hospital. Marked herniation in the operative area was noticed. Right facial weakness, spontaneous nystagmus in all directions, dilated and unequal pupils, generalized hypotonia with loss of all deep reflexes, and bilateral papilledema were found objectively. On August 17, a fragment of tumor tissue was removed through the old wound from the right cerebellar hemisphere. The patient died two days later.

*Necropsy Report.*—(Necropsy limited to cranium.) Gross Anatomy: The brain was removed through a small surgical opening. The pia-arachnoid showed no macroscopic changes. The gyri were flattened and in a few places showed slight elevations and increased consistency. At such areas, on incision, small nodules, measuring from 0.5 to 1 cm., were found, suggesting a small metastatic

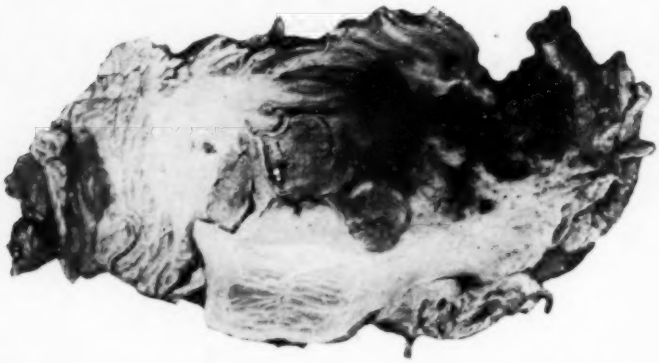

Fig. 16 (case 11).—Gross appearance of the tumor mass indicating extensive involvement of the cerebellum and compression of the fourth ventricle.

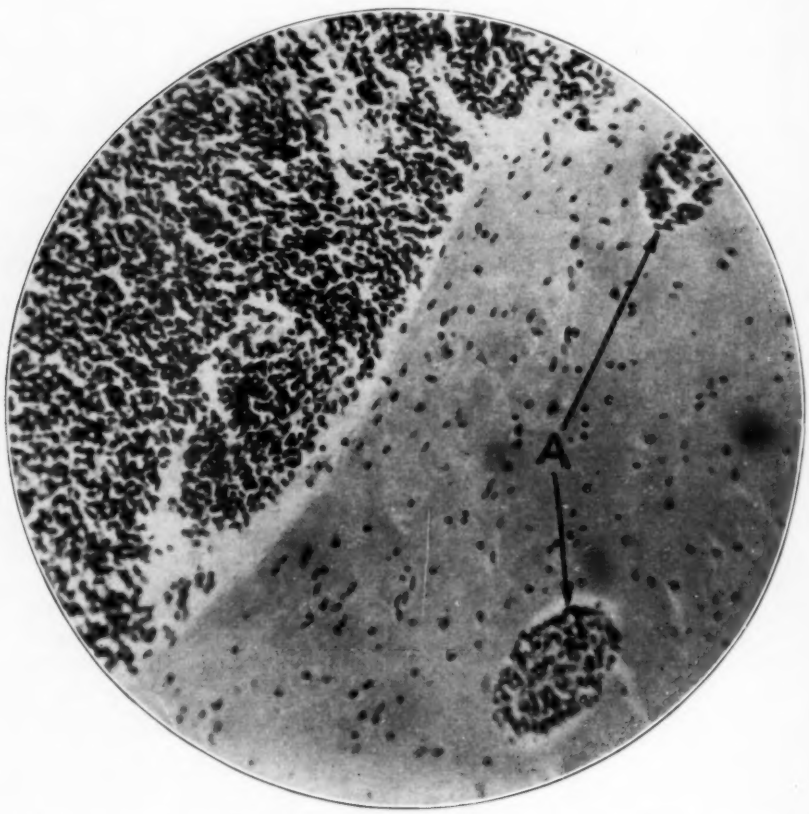


Fig. 17 (case 11).—Histologic appearance of a metastatic mass in another region (in a cerebral hemisphere). The adventitial infiltration (*A*) of adjacent blood vessels by tumor cells should be noted.

sarcoma. Nodules were found in the following situations: (1) left frontal lobe, anterior portion of upper frontal convolutions; (2) same convolutions, 2 cm. posterior to first nodule; (3) on the floor of the circular sulcus; (4) right occipital, and (5) cerebellum (fig. 16). The cerebellum was swollen, and the left lobe was extremely soft and fragile; at its upper surface it presented a hemorrhagic, apparently neoplastic, mass.

Microscopic Anatomy: Sections through the cerebellar tumor mass showed it to be highly vascular and cellular. There was little connective tissue stroma. Sections through the smaller tumor nodules showed rounded neoplastic masses, which were distinctly marked off from the rest of the brain tissue, and were made up of cells uniform in type (fig. 17). They were somewhat oblong in outline and rich in nuclear material, which stained deeply. The arrangement of the cells had a tendency toward whorl formation. The brain tissue directly adjacent to the neoplastic mass presented blood vessels, the adventitial spaces of which were infiltrated with a similar type of cell. In many instances such cells apparently had broken through the adventitial coat and had escaped into the extravascular space. The tumor mass itself had invaded the pia-arachnoid space and had extended into the contiguous brain substance by channels communicating with that space.

*Diagnosis.*—The condition was diagnosed as metastatic multiple sarcoma of the brain and meninges.

*Comment.*—No difficulty was experienced early in the clinical course in recognizing the neoplastic character of the lesion, for the signs of increased intracranial tension with rapidly developing bilateral papilledema pointed strongly in the direction of a cerebral tumor. The disseminated character of the lesion, evidenced by apparent involvement of the eighth and third cranial nerves, meningeal irritation and stem involvement, should have warned of the probably metastatic nature of the tumor.

The postmortem examination fully justified the postulated localization of the tumor in the posterior fossa as far as the main mass was concerned. However, there were other localizing signs, such as the left hemihypesthesia and hemihypalgesia, which should have suggested multiplicity of the lesions. The presence of bilateral papilledema bears out the assumption that neoplastic masses in the posterior fossa, with few exceptions, even though metastatic, will give rise to bilateral papilledema.

GROUP 5

CASE 12.—*Cerebral manifestations developed during the terminal stage of pulmonary disease. Rapid decline. Necropsy: Metastatic adenocarcinoma.*

*Clinical History.*—M. C., a man, aged 56, single, was admitted to the medical service of the Mount Sinai Hospital, June 1, 1923, complaining of rapid loss of weight, an annoying cough for the past three months, and shortness of breath for the past twelve days. The illness began five months previously with an increase in the severity of the cough, which had been present for about a year. The man was in bed for about five weeks and was then allowed to be up for three months. He continued to cough, lost weight rapidly, and more recently the left arm and the left side of the neck became swollen. The dyspnea became distressing.

*Examination.*—On admission, the patient presented irregular but active pupils; the ocular muscles were intact; the ocular fundi were normal. A mass, the size of a small hen's egg, was felt in the neck on the left side, just behind the inner aspect of the left clavicle. Over the left upper lobe of the lung and high up in the axilla anteriorly, there was marked dulness with diminished breath sounds

and an occasional moist râle. Two small nodules (neoplastic?) were also felt high up in the recti abdominis muscles. The patient was markedly cyanosed and showed pronounced clubbing of the fingers. Examination of the urine, spinal fluid and blood revealed normal characteristics.

*Course.*—The diagnosis of neoplasm of the lung with metastasis was made. Several hours after admission, the patient suddenly became unconscious, developed Cheyne-Stokes breathing, bilateral corneal anesthesia, conjugate deviation of the eyes to the left, and left hemiplegia with signs of involvement of the pyramidal

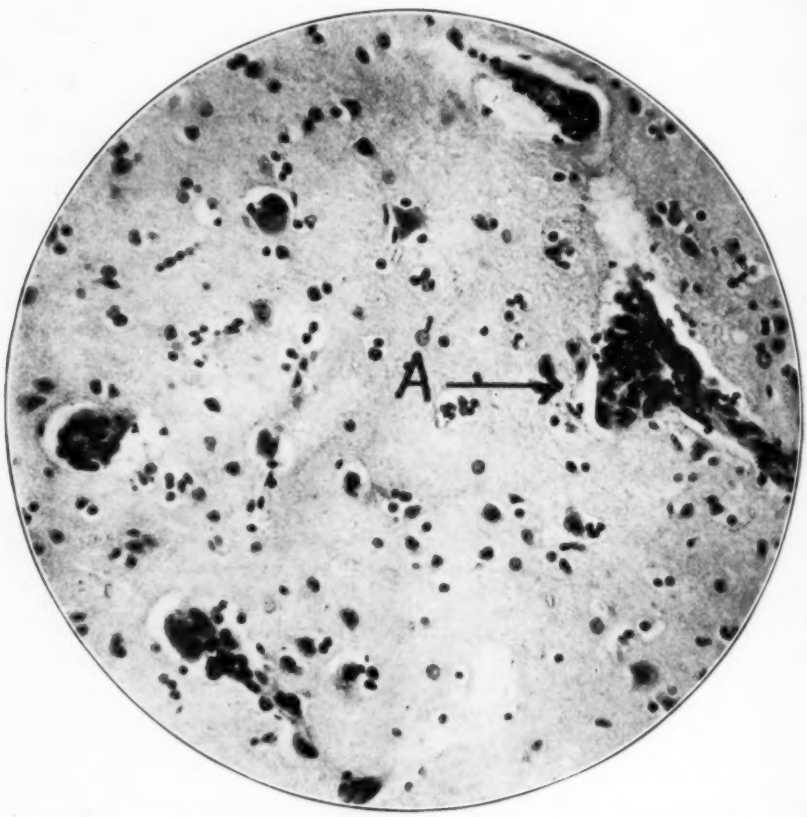


Fig. 18 (case 12).—Histologic features of tumors. The diffuse adventitial infiltration of blood vessels by tumor cells (*A*) should be noted.

tract on that side. The condition rapidly declined from that time. On the following day a complete quadriplegia with bilateral Babinski sign and lost abdominal reflexes developed. The man died without regaining consciousness on the third day in the hospital.

*Necropsy Report.*—Gross Anatomy: The meninges and cerebral cortex did not present any abnormalities. The base of the brain and the cranial nerves were normal. On section, the ventricles were normal in size, and no gross pathologic lesions were found in the brain substance.

Microscopic Anatomy: Sections through the cerebral cortex showed isolated areas in which carcinomatous cells had invaded the Virchow-Robin spaces of several small vessels (fig. 18). Aside from this, some selected sections from the brain stem showed mild degenerative changes in the parenchyma.

*Diagnosis.*—The condition was diagnosed as metastatic adenocarcinoma, primary in the suprarenal gland.

*Comment.*—In this case the cerebral manifestations appeared late in the clinical course, and there was little opportunity to study the neurologic features. It would appear, however, that the microscopic nature of the metastatic lesions is responsible for the rapidity with which the fatal issue occurred; in character such a lesion resembles one of diffuse encephalopathic origin. No further correlation between the anatomic and clinical observations can be made.

## SUMMARY AND CONCLUSIONS

In this paper, we have stressed mainly the clinical features of secondary tumors of the brain, and we shall not comment on the anatomic points of interest beyond making a few observations on the more apparent gross morphologic characteristics. In only four of the twelve cases reported were the metastatic foci single; in the others they were multiple, showing wide variations in number, size and distribution. The seat of the primary growth could not be determined in every instance, since in a large number of the cases the postmortem investigations were limited to the cranial cavity. With the aid of microscopic study the following organs have been established as the seats of the primary tumors: (1) the bronchus in cases 5 and 6; (2) the skin in cases 7, 8 and 9; (3) the suprarenal gland in case 12; (4) the prostate in case 4; (5) the urinary bladder in case 1; (6) the colon in cases 3 and 10. Cases 2 and 11 are the only two in the series in which the primary focus remained undetermined.

It is highly suggestive that in cases 5, 6, 8 and 12, either observations at autopsy or roentgen-ray studies have shown the thoracic cavity to be the seat of a neoplastic growth.

The finer cytologic features of the invading growths as well as in the adjacent brain tissue belong to a separate chapter in neuropathology. Because of that, and in view of the recent contribution on the histopathology of cerebral carcinoma by Hassin and Singer,[4] no further discussion of the histologic details will be undertaken here.

In the comments on each case we have attempted to correlate the clinical and the anatomic manifestations. Our impressions may be summed up in the following statement: The clinical signs and symptoms arising from metastatic tumors of the brain depend on: (1) the extent of involvement of the brain by the principal largest mass (cases 4, 8, 9

4. Hassin, G. B., and Singer, H. D.: A Contribution to the Histopathology of Cerebral Carcinoma, Arch. Neurol. & Psychiat. **8**:155 (Aug.) 1922.

and 10); (2) the presence of a mass, however small, in a vital part of the cerebrospinal axis (cases 3 and 5), and (3) the presence of a metastatic nodule so situated that it will obstruct the normal flow of cerebrospinal fluid (cases 2, 6 and 11). In any event, multiplicity of lesions will in the majority of cases lead to dissemination of objective signs.

The results of roentgen-ray examinations of the skull and thorax are also of interest in a number of our cases. Roentgenograms of the skull in all cases failed to reveal any destructive foci in the cranial bones. It is rather significant that, in our experience, secondary malignant tumors of the brain substance have uniformly spared the cranial bones, while, on the other hand, tumors that have metastasized into the cranial bones have not invaded the brain substance. Roentgenograms of the chest, however, showed an extensive neoplastic mass in case 6, which indicated the most probable location of the primary focus, and multiple circumscribed masses in the lung in case 8, which were undoubtedly secondary foci similar to those found in the brain.

Summing up the more constantly found clinical manifestations, we are tempted to regard the following as characteristic of metastatic tumors of the brain:

1. An acute and often precipitate onset of cerebral manifestations, commonly of a disjointed or disseminated character, simulating a meningo-encephalitic process, is found.

2. Symptoms of increased intracranial pressure, such as headache, nausea, vomiting and dizziness, which are usually out of proportion to the objective neurologic observations, occur.

3. Papilledema is not common; it usually occurs when a tumor mass obstructs the escape of cerebrospinal fluid from the lateral ventricles.

4. Meningeal signs, often associated with radicular pain, are not infrequent, and pleocytosis is occasionally found, probably as the result of direct invasion of either the subarachnoid space or the subependymal tissue by tumor cells.

5. The rapidly declining clinical course is characterized by the progressive appearance of new and poorly linked or diffuse signs and by general wasting and growing asthenia.

6. Psychotic manifestations were present, as a terminal event, in a limited number of our cases. In our opinion they have no diagnostic value beyond indicating widespread cellular reaction.

It is apparent that the clinical features enumerated are most commonly found in diffuse meningo-encephalitic lesions, and not infrequently in primary malignant tumors of the brain, particularly in the form of the primary malignant cerebral neoplasms as described by

Globus and Strauss.[5] The first can be ruled out often by the absence of febrile manifestations and negative serologic and roentgen-ray examinations. Primary malignant tumors differ from those under consideration by their tendency to manifest more localizing objective neurologic signs and by their more uniform clinical course.

It can be said, then, that an acute onset of cerebral symptoms, followed rapidly by the development of neurologic signs of a disseminated character and symptoms of increased intracranial tension, in the absence of changes in the disks, and positive serologic or febrile manifestations, suggests strongly a metastatic neoplastic process. The probability is strengthened further by the rapid evolution of neurologic signs and the appearance of progressive wasting and of asthenia out of proportion to that usually encountered in primary tumors of the brain. Under such circumstances search should be made for the primary malignant focus.

5. Globus, J. H., and Strauss, I.: Spongioblastoma: A Primary Malignant Tumor of the Brain, Arch. Neurol. & Psychiat. **14**:139 (Aug.) 1925.

## CORRECTION

In the article by Dr. A. J. McLean, "An Attempt to Identify the Central Cells Mediating Kinesthetic Sense in the Extrinsic Eye Muscle" (ARCH. NEUROL. AND PSYCHIAT. **17**:285 [March] 1927), some of the legends are under the wrong illustrations. The legend appearing under figure 5 should be under figure 6; that under figure 6 should be under figure 7, and that under figure 7 should be under figure 5.

It of course is obvious that figure 1 is upside down.

SPECIAL ARTICLE

# RECENT WORK OF PAWLOW AND HIS PUPILS

## CONDITIONED REFLEXES; SYMPATHETIC NERVOUS SYSTEM (ORBELI); EPILEPSY AND CEREBROSPINAL FLUID (SPERANSKY)

W. HORSLEY GANTT, M.D.
LENINGRAD, RUSSIA

The following is a sketch of the work of Professor Pawlow on conditioned reflexes, of Orbeli on the sympathetic nervous system, and of the new work of Speransky on pathology of the brain.

As Pawlow's two books [1] are soon to appear in English, what I have to say about his work is in no way intended as a comprehensive review. On the other hand, I desire to call attention to Pawlow's achievements in this field—so long obscure; perhaps the personal experience of one who is not a specialist in this question, but who has learned the Pawlow method first hand may help to clarify this intricate subject. Let it be said at the outset that, although it is easy to grasp the principles on which the work of conditioned reflexes has been built and to understand a simple experiment, the comprehension of the whole subject is extremely difficult. I am in agreement with the opinion in the Pawlow laboratories after two years of work there—that besides Pawlow, there are few, if any, even his own pupils, who are capable of giving a complete exposition of the work in all its ramifications. The longer one is acquainted with Pawlow and his work, the greater becomes one's conviction that it is he who has been entirely responsible for its success.

### CONDITIONED REFLEXES

Pawlow, who considers all acts as reflex, distinguishes between two kinds: the simple physiologic reflex, inborn and unalterable, and the more complicated reactions, usually called psychic, which are acquired and formed only under certain conditions. The former are his unconditioned, the latter his conditioned reflexes.

Seeing the psychic flow of saliva, Pawlow was not satisfied to explain this in the vague and meaningless terminology of psychology but sought a method of measuring this psychic activity. For this purpose he felt that the salivary glands were admirably adapted to his new work; [2] they

1. These books deal with work on the brain by the method of conditioned reflexes. They are now in the course of publication in the English language. The first, "Conditioned Reflexes," will be published by the International Publishing Company, New York; and the other, "Activity of the Cerebral Hemispheres," translated by Dr. G. V. Anrep, will be published by the Oxford University Press.

2. Anrep, G. V.: Proc. Roy. Soc. London, *B*, **94**:405, 1923.

are closely connected with the unconditioned food reflex, and the food reflex can be connected by coincidence with a large number of diverse stimuli, such as the ringing of a bell, the sight of a lamp, irritation of the skin or application of cold. After a number of associations, these conditioned stimuli come to produce a flow of saliva even without the presence of the original unconditioned stimulus (food). Thus the flow of saliva resulting from the sound of a bell alone, because it formerly accompanied feeding, is a conditioned reflex in contradistinction to the inborn (unconditioned) reflex.

METHOD

It was Pawlow's next idea to measure these processes set up by the various stimuli—taste of food (unconditioned), or bell, light, odor, touch (conditioned) stimulus, with which the unconditioned reflex had been connected by association. To do this he devised a method of making a salivary fistula so that the fall of each drop of saliva could be recorded, and he chose the dog for this work, "the faithful companion of man for ages," as he says. With the aid of Hannecke, he has worked out a delicate apparatus for carrying on these experiments. Doubtless their success is the result, largely, of the mechanical perfection of the apparatus. His new laboratory is devised so as to eliminate every external stimulus from the dog except that given by the experimenter. The building is surrounded by a moat several feet deep, filled with sawdust to prevent vibrations from the street. Furthermore, the arrangement of the working chamber isolates the operator and dog from the outside world and from one another. The eight working rooms are widely separated, occupying only the corners of the building, and the upper rooms are separated from the lower by an intervening story. The walls of the eight chambers are 2 feet thick, and admission is through double iron doors, padded with rubber, like those of a large bank vault. The operator sits in an outer room. Within this outer room is the dog's cell, which also has double walls and concrete doors, 8 inches thick, rubber padded and with large iron bars. The dog's cell consists of two concrete shells, the walls of each being 8 inches thick. The inner concrete shell is separated from the outer by a 6 inch air jacket and is in contact nowhere with the outer shell, being suspended from the roof of the other shell by a huge iron hook. When the doors are closed, the dog on its stand is completely isolated from the vibrations, sights and sounds of the outside world. The experimenter sits at a table on the outside of the dog's cell, facing an electric switchboard, by which he may, by pressing a button, give the dog any desired conditioning stimulus—a skin irritation, a light, a metronome, a whistle or an application of cold. He may also feed the dog (unconditioned stimulus). The response of the dog is measured through the flow of saliva from its parotid fistula, to which is attached a reservoir

communicating with a manometer on the outside of the cell in front of the operator, capable of registering one-tenth drop. The manometer may be connected further with a recording drum on which is written the number of drops in tenths.[3] The operator may observe the dog through a periscope.

Such complete isolation is useful in those experiments in which the dog has to discriminate between delicate sounds, etc., but for many experiments one can use an ordinary room for the dog with the operator seated outside at the electric board and manometer.

Although Pawlow uses the food reflex as the unconditioned reflex in most experiments, a movement reflex may be used, such as the withdrawing of a paw when electrically shocked. Of course, the conditioned stimulus may be the same in both cases. If the conditioned stimulus is the metronome of 120 beats, when this metronome starts the dog will either secrete saliva or howl and jerk up its foot, depending on whether this stimulus has been connected with the food or the motor reflex.

In order to form the conditioned reflex, the conditioned stimulus must be associated with the unconditioned stimulus a certain number of times (twenty or more, depending on the dog and other conditions). Pawlow has found that the conditioned stimulus must always precede the unconditioned. For example, if the metronome follows the food by five seconds instead of preceding it, the metronome does not develop the power of producing a flow of saliva. This is probably because the brain process, excited by eating, is strong enough to keep out stimuli from the receptor organs.

The metronome, or other stimulus that has always been associated with food, becomes a positive stimulus, although when first used it was an indifferent one. Another metronome, e. g., 150 beats, when first used in a dog with a conditioned reflex on a metronome of 120 beats, also produces a flow of saliva, because of the common qualities of the stimulus. However, if this metronome 150 is repeatedly used without food, the dog comes to differentiate between the two. Metronome 150 becomes a negative conditioned stimulus; it calls forth in the dog having a positive conditioned reflex on metronome 120 an active inhibition. The closer the rates of the two metronomes, the greater the inhibition necessary to prevent flow of saliva on the negative metronome.

Instead of using metronomes, two points on the skin may be irritated, one for the positive and the other for the negative conditioned stimulus; or two lights differing in intensity, color,[4] position, etc., or heat and cold, odors (camphor and tincture of valerian), or different chords on a

3. Details of this apparatus are described by Anrep, G. V.: J. Physiol. **53**:367 (May) 1920.

4. The differentiation of color has not been obtained in all cases, and Pawlow thinks there may be color blindness among dogs.

pipe organ may be used. With the negative stimulus, there may be a slight response because inhibition is not complete.

Some of the theories worked out by Pawlow need new terms, such as: "analyzer, inhibition, irradiation, delayed reflex, trace reflex, chain reflex, induction in the brain."

Analyzer is the term given by Pawlow to include not only the receiving sense organ, but its brain connections, whereby it can discriminate between unimportant and important stimuli. Thus there is the eye analyzer, the skin analyzer, the ear analyzer, etc.

Inhibition may be internal or external;[5] it may be local or spread over the whole brain, resulting in sleep. This occurs in dogs when the same stimulus is repeated too often without alternating it with other stimuli, so that a given analyzer becomes fatigued, or when the stimulus is too intense or disagreeable (often in skin irritations). If a positive conditioned stimulus, i. e., one which always has been followed by feeding, is given and feeding withheld for more than thirty seconds, the conditioned reflex is delayed; inhibition occurs during this interval and prevents a flow of saliva, but if some indifferent stimulus is given during this interval, the inhibition is inhibited, the brake is lifted, and saliva begins to flow. If the feeding does not follow for some minutes after the end of the conditioned stimulus (e. g., four minutes), the conditioned reflex—the flow of saliva—is delayed for three minutes; it becomes a trace reflex, as the flow of saliva now comes on the trace or memory of the conditioned stimulus. Conditioned reflexes have also been formed on time intervals.

Induction is used in relation to conditioned reflexes in somewhat the same sense as Sherrington's spinal induction. This subject has been elucidated by Foorsikov in Pawlow's laboratory. The following example will illustrate: A dog that has a positive conditioned reflex on metronome 120 gives five drops of saliva in ten seconds on this conditioned stimulus. If a few minutes before trying this conditioned stimulus one uses a negative conditioned stimulus and a few seconds later tries metronome 120, the positive conditioned reflex is greater, e. g., seven drops, because it follows the negative stimulus. Vice versa, a negative conditioned stimulus has a stronger inhibiting effect when it has been just preceded by a positive conditioned stimulus.

Reflexes of higher orders have been worked out as follows (Foorsikov): In a dog a positive conditioned reflex is formed on a light, food being used as the unconditioned stimulus. Several times a day the light is turned on, and at the same time a whistle is blown, and this combination is not supported by feeding. Soon the whistle acquires the character of the positive conditioned stimulus because of

5. These facts are dealt with briefly here because they are recorded in the paper by Walshe.

its association with the positive light; i. e., the whistle sounded alone produces a flow of saliva, although the whistle has never been followed by feeding. The whistle is called the reflex of the second order.

By the use of a defense reflex, the work has been carried a step further. An electric current (unconditioned stimulus) is passed through the foot of the dog; it howls and draws up its foot (unconditioned reflex). The current is then preceded by a skin irritator (conditioned stimulus) and, after some repetitions, the conditioned stimulus alone produces the howling and movement of the foot (conditioned reflex). Now the skin irritation is combined several times daily with the sound of bubbling air through water, but without the electric current. Soon the bubbling sound alone acquires the character of a positive conditioned stimulus, i. e., it evokes the howling and the movement of the dog's foot, though it has never been combined itself with the electric current. This is a reflex of the second order. Now the bubbling is repeated simultaneously with a whistle for several days. Soon the whistle acquires the property of the conditioned stimulus; it causes the dog to howl and draw up its foot. It is a conditioned reflex of the third order. Higher orders have not been formed.

Inhibitory conditioned reflexes of higher orders have been formed in a similar manner; i. e., by associating an indifferent stimulus with a negative conditioned stimulus. The indifferent stimulus takes on the quality of the negative conditioned stimulus. This leads to the deduction that inhibition and stimulation are different sides of the same process. Of great interest is the work indicating that the brain functions as a mosaic of inhibition and excitation points.[6] Seriatsky formed a series of positive conditioned reflexes with tones of a pipe organ, alternating with a series of negative conditioned reflexes, i. e., a positive conditioned reflex on the note C 512 (followed by food), a negative conditioned reflex on the note three tones lower and three tones higher (not followed by food), and another positive conditioned reflex three tones higher than this, until the whole keyboard of five octaves was used up. This is a rhythmic mosaic, as the excitation and inhibition points are equidistant. In a second dog a positive and a negative conditioned reflex were formed at unequal distances on the keyboard, i. e., a positive on 363 vibrations and a negative one note lower, another positive two notes lower, another negative one and one-half notes lower, etc. This is an arrythmic mosaic. It was much more difficult to form and was often followed by neurasthenic symptoms in the dog.

A year after forming six excitation and six inhibition points at regular intervals, the effect of those tones lying beyond the limits, i. e., higher and lower than the original twelve notes, was tried. It was

6. This work was performed by one of Pawlow's younger pupils, V. V. Seriatsky, who died in April, 1926.

found that these notes were preformed positive or negative points, following the same regular rhythm as the original notes; that is, they produced a flow of saliva (though they had never been accompanied by food) or they produced inhibition, depending on their position on the scale.

What is the nature of the tones lying between the positive and the negative notes? It was found that their nature depended on their position—those on either side of the positive were also positive, and those adjacent to the negative were also negative. According to Seriatsky, "Thus excitation and inhibition zones were formed in the cortex, and the territory of each of these spread to the extent of six semi-tones." After six months the inhibition zones had encroached on the excitation zones, so that each occupied twelve semitones instead of six. At the end of a year, the inhibition fields had become indifferent.

An interesting effect was noted by frequent successive repetitions of positive conditioned stimuli, not interrupted by other stimuli: the dog became irritable and excited. On the other hand, if only negative conditioned stimuli were used, the dog became sleepy, and after several repetitions, folded its paws and fell asleep.

Seriatsky said:

> The cortex of the large hemispheres as regards its functional powers must present an example of an exceptionally delicate and variegated mosaic, enormous in its dimensions and complexity. This mosaic consists of various excitation, inhibition and indifferent points which are closely interlayed with one another, and possess the quality of slowly concentrating during life. The ultimate aim of the brain is to break up the previously irradiated processes into a series of excitation and inhibition partitions. We do not consider this mosaic as constant, motionless and fixed. On the contrary, we believe that it undergoes a constant change depending on the surroundings, etc.

## NEURASTHENIA

The production and treatment of neurasthenia in dogs has recently been studied in Pawlow's laboratory by Seriatsky, Federoff and Petrova. The symptoms were produced by repeating too often, without intervals for rest, a conditioned stimulus, or by presenting a problem of too difficult differentiation. For example, if the dog is given metronome 100 as a positive conditioned stimulus (followed by food) and metronome 110 as a negative conditioned stimulus (not followed by food), the intervening beats, e. g., metronome 104, being close to metronome 100, will require much inhibition from the dog to prevent a flow of saliva. As Dr. Volborth explained to me, when metronome 100 is followed by metronome 104 (while inhibition has not had time to disappear), there is a collision between the positive and negative processes, which results in an abnormal state, giving symptoms similar to neurasthenia. These dogs whine, refuse to eat, show a disinclination for their daily

work, etc. Such dogs recovered with rest and rectal injection of potassium bromide given just before the experiments. Whether the symptoms will tend toward sleep and depression or excitation depends on the type of dog. Normally, these processes of excitation and inhibition are in equilibrium. Induction prevents spreading of a single process, because around an area of excitation is a zone of inhibition which walls in the excitation process and prevents its spreading.

### EFFECTS OF REMOVAL OF THE BRAIN

The removal of the frontal half of the cortex appeared more injurious than the removal of the posterior half. Animals with the whole cortex removed fare better, probably because the spinal reflexes are free to act. In partial extirpation of different regions of the brain, there may be partial compensation by the remaining parts. When the cortex of a cerebral hemisphere is removed, it is impossible to form the defensive conditioned reflex. In such an animal a strong electric current applied to the foot caused only a chaotic defensive reflex, beginning on the sound side and extending to the other. A conditioned reflex did not form after 250 combinations of the conditioned stimulus with the electric current.

### CONDITIONED REFLEXES IN OTHER ANIMALS

Conditioned reflexes have been formed not only in dogs but in such diverse animals as fish, mice, puppies and children by Pawlow's method. A tank of water enclosed in a cabinet is used for work with fish. Inside this cabinet are red and green electric lights, a metronome, etc. The unconditioned reflex is the motor response to an electric current sent through the clamp holding the fish. The conditioned stimulus may be light, metronome, etc. A red light may be used for a positive conditioned stimulus (given before the electric current) and a green light for a negative conditioned stimulus (not followed by a current). After a large number of trials, the fish jumps (conditioned reflex) when it sees the red light (conditioned stimulus), but not the green. The motor response of the fish is recorded on a drum outside the cabinet.

The apparatus for forming conditioned reflexes in mice is ingenious and was perfected by Hannicke. When a given bell sounds, the mice run to a certain place to get food, and in going there they have to cross a platform attached to springs. When they step on this platform, the movement is registered on a revolving drum. A revision of the former work on the inheritance of conditioned reflexes is being carried out with this entirely new apparatus. A clock arrangement makes twenty electric contacts during the night. These ring a bell, and a few moments later open a valve which allows grain to drop into a certain room of each cage. When the bell rings, one sees the general migration of the mice into the "dining room." The mice are never fed without the bell.

Males and females are kept in separate cages so that the number of oncoming generations can be carefully regulated. When an experiment is to be made, the mice are removed to a special cage in which the results can be registered automatically.

### WORK OF KRASNOGORSKI ON CHILDREN

The work of Krasnogorski in the Children's Clinic of the Medical Institute (Filatov Hospital) deserves mention here. Krasnogorski is one of Pawlow's older pupils and Pawlow confers with him frequently. He published his first work on conditioned reflexes in children in 1907.[7] He has twelve physicians working under him on the subject, and three well equipped rooms for the study of conditioned reflexes in children. He has received money from the Soviet government for three additional rooms.[8]

Children develop conditioned reflexes much more quickly than the dog—from ten to twenty-five trials compared to the dog's thirty to 100; they retain them much longer and more strongly than the dog without intervening practice; they can be destroyed more quickly in the child, e. g., when a positive conditioned stimulus is repeated several times without being supported by food.

Krasnogorski uses children aged from 1 to 5 years. He has found it impossible to develop conditioned reflexes in infants less than 2 weeks old. In children under 1 year, the mechanical irritation of the skin is not specific. The skin analyzer begins to function at about 3 months. At the age of 7 months, the child differentiates between red and white light and at 8 months between odors of camphor and cologne. The movement analyzer appears at 6 months of age.

Krasnogorski has shown the clinical importance of conditioned reflexes; abnormalities indicate a disturbance in the balance between inhibition and stimulation. His work gives a rational basis for classification and treatment of neuroses. He suggests its use also as the basis for child education. In 1925, he told me that he had found by his method of conditioned reflexes that an idiot child in his clinic had a brain on the level of a fish; i. e., it was as slow as the fish in forming conditioned reflexes. In myxedema, epilepsy and neuroses, internal inhibition develops in the child. Imbeciles developed conditioned reflexes with difficulty, but some neurotic children develop them more quickly and lose them more quickly than a normal child. Leonov, in Krasnogorski's laboratory, found in rachitic children that the movement, taste and smell analyzers are disturbed; orientation and adaptation

7. Krasnogorski, N. I.: Russk. Vrach, no. 36,907, 1907.

8. Kroll, M.: Jahresb. d. ges. Neurol., 1922; Krasnogorski, N. I.: Rev. de méd. **40**:294 (May) 1923; Der Schlaf und die Hemmung, Monatschr. f. Kinderh. **25**:372 (March) 1923.

are weak; motor reflexes are slowly formed, but when once formed disappear slowly.[9]

COMMENT

The actual work on conditioned reflexes is not nearly so simple as it would seem from the description. The dogs, as a rule, are easy to work with, and remain quiet during the experiment; they seem to enjoy the work (except when it is extremely difficult), and run and jump on their stands with as much zest as they might show during a rabbit hunt.

As an illustration of some of the pitfalls, I shall describe what happened in one of my dogs. A dog that had never been worked with before was assigned to me. Before I could begin working out a problem, it was first necessary to form some conditioned reflexes in the dog. For this purpose, I was to work one hour daily with the dog for five or six days in the week. The dog was quiet, stood well in its harness, and did not object to having the glass reservoir fastened (with a modified sealing wax) over the opening of its salivary fistula. The first conditioned stimulus I used was a metronome of 120 beats. After from five to thirty seconds, I followed the metronome with food. The interval between the conditioned stimuli (metronome) was from five to fifteen minutes. The dog was clever, and after thirty trials began to secrete saliva on hearing the metronome. Then I used a whistle and later a skin irritator as conditioned stimuli. The latter, I noticed, was the weakest. It took much longer before it developed the power of producing a secretion of saliva and seemed to divert the dog's attention, although it was not in the least painful. In order to strengthen this effect, as I thought, I employed it more frequently than the others. In a week, however, this led to disastrous results. Being used too often, the skin irritator became a negative conditioned stimulus instead of positive as I desired, setting up inhibition instead of stimulation, because the skin analyzer became fatigued. The skin analyzer, as I did not know then, is more easily fatigued than the ear or eye analyzer. After the skin irritator was used, the dog, instead of secreting saliva, became apathetic and drowsy and frequently would not eat until I entered the room and gave it food from my hand, thus arousing it from its state of inhibition. After several months' work this animal had to be rejected entirely. As Dr. Volborth expressed it to me, "The difficulty of the problem is not in the mechanical work, but in maintaining a proper equilibrium between inhibition and excitation in the brain. For this, very careful judgment, experience, and extreme vigilance are necessary in every experiment."

9. For further description of conditioned reflexes in neurotic children, see Krasnogorski, N. I.: Conditioned Reflexes and Children's Neuroses, Am. J. Dis. Child. **30**:753 (Dec.) 1925.

## WORK OF ORBELI ON THE SYMPATHETIC NERVOUS SYSTEM

Much work has been done recently in the laboratory of Orbeli on the function of the sympathetic nervous system. This has been mentioned in Stanley Cobb's review on the tonus of skeletal muscle,[10] and also in the *British Medical Journal*. Since Cobb's review, more work has appeared, an account of which I give here. I am grateful to Professor Orbeli for giving me permission to include his unpublished work, and for having read over the description that I submit here.

The influence of the sympathetic nervous system on spinal reflexes in the frog has also been studied. The spinal cord was cut in the occiptal foramen, and the brain was destroyed. The aorta was tied at the junction of the arches. The sympathetic trunk on one side was taken on a ligature and cut through at the level of the fifth to sixth ganglia so that the peripheral end could be stimulated. The rami communicantes to all the upper nerves were cut, leaving the sympathetic on the ligature in connection only with the plexus lumbalis through the rami communicantes of the eighth, ninth and tenth spinal nerves. On the other side, all the rami communicantes were sectioned.

The experiment was performed an hour later. The reflex irritability of the spinal cord was tried every five minutes, according to the method of Turk (i. e., both hind feet were dipped in a 1 per cent solution of sulphuric acid and then rinsed with water). The reaction time—the time between dipping the feet in the acid and their withdrawal—was reckoned with a metronome. After the reflex had been tried several times in this manner, the sympathetic trunk on the ligature was stimulated (four minutes after the last trial), either through an interrupted induction current lasting one minute or by chemical stimulation (0.1 per cent nicotine), with the following results: (1) bilateral lengthening of the reaction time; (2) bilateral acceleration of the reaction time; (3) acceleration of the reaction time only on the stimulated side; (4) lengthening of the reaction time on the stimulated side; (5) lengthening of the reaction time on the side opposite the stimulated side. These results were corroborated in a completely bled preparation of a spinal frog, in which all the viscera together with the heart were removed, and also in a decapitated toad after removal of all the viscera and after opening the spinal canal so that the spinal cord, denuded of part of its covering, lay free in the spinal canal.

On the strength of these facts, Orbeli avers that the efferent sympathetic fibers have a direct influence on the central part of the spinal reflex arc. The possibility of the influence on the peripheral receptors is not excluded.[11]

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10. Cobb, Stanley: Physiol. Rev. **5**:534 (Oct.) 1925; Brit. M. J., Sept. 20, 1924, p. 533; A Medical Review of Soviet Russia. VI, Brit. M. J., in press, 1927.

11. Translation from Russian J. Physiol., 1926, vol. 8.

### INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE ACTIVITY OF MUSCLE FATIGUED UNDER AN ANAEROBIC CONDITION

The following experiments were made by Ginetzinsky in an atmosphere of hydrogen: The motor roots of the eighth and ninth nerves were stimulated by single maximal break shocks (from thirty to forty times a minute). At the moment of the development of fatigue, the sympathetic cord was stimulated with an interrupted current, and the contraction of the gastrocnemius muscle was increased as in an atmosphere of air. Thus it follows that the effect provoked in the skeletal muscle by stimulation of the sympathetic nervous system cannot be explained exclusively by sympathetic augmentation of oxidation of the products of metabolism.[12]

### EFFECT OF THE SYMPATHETIC NERVOUS SYSTEM ON THE PERIPHERAL APPARATUS OF THE MOTOR NERVE

The gastrocnemius muscle of the frog was fatigued by single induction shocks sent alternately through the motor roots of the eighth and ninth nerve, and then through the muscle itself. If the sympathetic system was stimulated, the contraction provoked by the indirect stimulation was sharply increased, and the curve of fatigue from the direct stimulation remained unchanged.

In another series of experiments, the sartorius muscle of the frog was immersed in Ringer's solution, which was replaced at a certain moment by a 0.25 per cent solution of chloral hydrate. The excitability for maximal induced currents was tried every minute, the current being applied to the motor roots of the nerve or to the muscle itself. Usually, in the replacement of pure Ringer's solution for Ringer's chloral hydrate, the height of the contraction provoked by direct and indirect irritation was equally decreased, and after fifteen minutes showed a complete loss of excitability for the indirect stimulation, and only slight contraction with direct stimulation. If, under these conditions, the sympathetic trunk was stimulated, the indirect excitability in certain cases fell quickly to zero; in others, on the other hand, it rose just as quickly; the direct excitability remained without change.

Orbeli concludes, therefore, that the sympathetic effect in the skeletal muscle takes place in the peripheral apparatus of the motor nerve.[13]

### THE PSEUDOMOTOR (TONOMOTOR) LINGUAL EFFECT OF THE SYMPATHETIC AND HYPOGLOSSAL NERVES

The hypoglossus was cut in several dogs in the osseous canal, just above its junction with the sympathetic fibers originating from the

12. Unpublished work.
13. Unpublished work.

superior cervical ganglion. Several days after this operation, the pseudomotor effect of the lingual nerve on the musculature of the tongue was exactly as clearly marked as after the usual peripheral section. If now, immediately before the lingual stimulation, the cervical sympathetic nerve is stimulated, there is a marked increase of the pseudomotor effect with lowering of the threshold of irritation, strengthening of the tonic contraction, shortening of the latent period and lengthening of the residual contraction. On the contrary, an outspoken lessening of the lingual effect, many times even to the point of complete inhibition, is produced by the stimulation of the hypoglossal trunk just below the section (i. e., the stimulation of the real bulbar hypoglossal fibers).

Orbeli summarizes his work as follows: The sympathetic nervous system exerts a profound influence over the physicochemical changes occurring in skeletal muscle, accompanied by a modification of the functional ability of that muscle. These changes influence, it seems, the conditions of the motor end-plate, calling forth transformations in the efficiency of the corresponding muscles. This forms a sort of regulatory mechanism for the expenditure of muscle strength, and governs the condition of impulses by the motor nerves. From this point of view, the sympathetic innervation of skeletal muscle is an adaptive innervation through which the functional ability of the muscle is determined.

## SPERANSKY'S WORK ON EPILEPSY AND ON THE CEREBROSPINAL FLUID

Dr. A. D. Speransky, formerly a surgeon, who for the past three years has been working with Pawlow, finished work in 1925 that showed the following: (1) Slight freezing of the dog's cerebral cortex causes epileptic convulsions after from two to five hours, followed by death in from twelve to fifty hours. (2) The result is the same regardless of the portion frozen, with the exception of the motor region. (3.) If the frozen part is removed immediately after freezing, no symptoms result. (4) If, on the other hand, the frozen part is not removed until after the onset of symptoms, death is not always prevented. (5) Transplantation of a part of the frozen brain to the subdural space of a healthy dog causes symptoms of epilepsy and death. (6) Subcortical symptoms are the first to appear after freezing and the last to disappear.

Speransky thinks that an autoneurotoxin is formed, which passes into the blood, producing hyperkinetic symptoms. An intense motor excitement, although not epilepsy, is produced by injection of from 150 to 300 cc. of defibrinated blood from the ill animal into the blood of a healthy dog. Immunization against the symptoms of freezing has been tried with some success; i. e., freezing the brain gradually in increasing "doses." Attempts to immunize by subcutaneous injection of an emulsion of the frozen brain of a dying animal were without results, but if

this frozen brain emulsion was injected subdurally in a healthy dog, it later could withstand larger "doses" of freezing.

Following up this idea (that an autotoxin is formed by freezing the brain) and related facts (such as the production of a lesion in the opposite testicle when one of the testicles is frozen), Speransky proposes to study the effect of freezing malignant tumors.[14]

### INFLUENCE OF THE CEREBROSPINAL FLUID ON PHYSIOLOGIC AND PATHOLOGIC PROCESSES IN THE BRAIN

Speransky, working on the properties of the autoneurotoxins formed by freezing parts of the living brain in dogs, observed that in the transfer of parts of the brain of the ill dogs to the meninges of healthy dogs there was absorption of the transplanted parts without reaction in the surrounding tissues. The disappearance of the transplants is not accompanied with adhesions between the dura and pia mater. Not a trace of any kind remains on these membranes—not any thickening or pathologic change that might show that there was a reaction of the vessels.

Supposing that the dissolution took place through the agency of the cerebrospinal fluid, the author performed the following experiments in vitro: Pieces of the brain of the dog or mouse (from 7 to 8 mm. thick and 2 by 2 mm. broad) were placed in a fresh extract of cerebrospinal fluid of the dog in the thermostat at from 39 to 40 C. For control, such pieces were placed in physiologic sodium chloride solution or fresh blood serum of the dog. Every hour the tubes were shaken. After twelve hours the pieces of the brain in the cerebrospinal fluid fell to pieces, became finely divided, the liquid became muddy and there was a flaky sediment. After from twenty-four to thirty-six hours, all the pieces had been transformed into turbid fluid and flaky sediment. But in the blood serum and physiologic sodium chloride solution, the pieces of the brain began to dissolve only at the end of the third day, and even after five days the dissolution was not complete. Further experiments showed that egg white, blood fibrin and boiled brain are not changed in the cerebrospinal fluid. Only the fresh or frozen brain is dissolved. It was also shown that in the dissolving pieces of brain only the brain substance itself is split off. The pia and blood vessels maintain their resistance for a long time after the brain substance has disappeared entirely.

From this, Speransky deduces that in the cerebrospinal fluid only those albumins which enter the composition of the brain tissue are decomposed. The other albumins are not changed or are changed slowly.

As the bacterial toxins appear closer in their chemical nature to the albumins, and consequently should not be quickly destroyed in cerebrospinal fluid, the following experiment was proposed: A mixture of

14. Speransky, A. D.: Compt. rend. Soc. de biol. **94**:262 (Feb. 5) 1926.

tetanus toxin and brain emulsion was taken in the proportion according to Wassermann so that all the toxin should be completely neutralized. To one part of this mixture was added increasingly a few grams of cerebrospinal fluid of the dog; both parts were placed in the thermostat for from five to six hours. The subsequent introduction of these mixtures into the brains of more than thirty pigs, mice and dogs showed that the Wassermann mixture plus cerebrospinal fluid caused tetanus, whereas the introduction of a pure Wassermann mixture did not cause any disturbance in the animal. Further experiments showed that the autodigestion of dead and vital brain was the same as the autodigestion of the dead and vital stomach. It was shown that in the frozen portions of the cortex of dogs, neurotoxins developed, perhaps products of incomplete combustion. These products reach the cerebrospinal fluid in large quantities. The introduction of such toxic cerebrospinal fluid beneath the dura mater of a healthy dog gives the same symptoms as freezing the cortex.

The clinical and pathologic appearances caused by the subdural introduction of the toxic cerebrospinal fluid were the same as those seen after freezing the cortex but were more weakly expressed. Withdrawing of the cerebrospinal fluid from the sac of the dura mater immediately before the freezing of the brain causes a sharp delay in the reaction. If the withdrawal is done two or three hours after the freezing, the development of the symptoms is not prevened, and the animals die.

Speransky concludes:

> In local disease of the nervous system a destruction of the brain substance occurs in the affected parts. Parts of the products of the incomplete combustion arising from this destruction are transported into the cerebrospinal fluid, and through it poison the brain. In such a way local disease becomes general, and to this we owe the mechanism of the development of diffuse encephalitis.
>
> The greatest quantity of cerebrospinal fluid comes into relation with the brain substance in the ventricles. This explains the development of subcortical symptoms. The undamaged pia mater gives protection to the brain substance better than the ependyma; thus subcortical destruction often occurs earlier than the cortical.
>
> The pathologicanatomic changes in the brain and the clinical symptoms in all toxic encephalitis, as tetanus, hydrophobia, diphtheria, epidemic encephalitis and toxic encephalitis from freezing the brain cortex, have many things in common. In all of these the parts of the brain lying in the vicinity of the ventricles are affected; in all are observed changes in the cornu ammonis; in all there is an infiltration of the shallow parts of the brain substance, near the ependyma, and a thickening of the ependyma; the brain substance in nearly all of these cases has an infiltration in a circle of cells, not around the blood vessels as was formerly asserted, but around their adventitial sheaths which are filled with cerebrospinal fluid. Thus there is an organization of defense proceeding from the side of the cerebrospinal fluid.

All these facts lead Speransky to believe that the mechanism of development of all toxic encephalitis is one and the same. Although

different parts of the brain differ in their sensitiveness to different injurious agents, not all the changes depend on this specific sensitiveness. The constant changes that occur in the cornu ammonis, encountered in the diseases mentioned in the foregoing and in epilepsy, occur because this part of the brain is bathed on three sides with the cerebrospinal fluid. The subcortical parts are affected because of their proximity to the ventricles.

Speransky recommends careful study of the cerebrospinal fluid, of its ferments and its hydrogen ion concentration. He says that every change in this concentration is evidence of changes in the fermentive processes. There should first be a study of such processes as flow rhythmically with a periodic improvement and relapse—epilepsy, sclerosis disseminata, cyclic psychosis, etc. In the further study of such processes as tetantus and epidemic encephalitis, it is necessary to consider carefully the part played by the cerebrospinal fluid.[15]

15. This account of Speransky's unpublished work has been translated from an original account which he was kind enough to hand to me.

# News and Comment

## NATIONAL ASSOCIATION FOR THE STUDY OF EPILEPSY

The National Association for the Study of Epilepsy will hold its annual meeting at the Hotel Sinton, Cincinnati, May 30 and 31, 1927, immediately preceeding the meeting of the American Psychiatric Association. Papers will be read by Drs. Thomas B. Bass, Abilene, Tex.; L. Pierce Clark, New York; George Donohoe, Cherokee, Ia.; Morgan B. Hodskins, Palmer, Mass.; Albert G. Odell, Clifton Springs, N. Y.; John Notkin, New York; Harold A. Patterson, Sonyea, N. Y.; Lewis J. Pollock, Chicago; William T. Shanahan, Sonyea, N. Y.; Edward A. Sharp, Buffalo; Andrew L. Skoog, Kansas City., Mo.; H. C. Syz, Baltimore, and others.

The officers of the association are: Dr. G. Kirby Collier, Rochester, N. Y., President; Dr. A. L. Shaw, Utica, N. Y., Secretary and Treasurer.

# Abstracts from Current Literature

ANATOMIC CONTRIBUTION TO THE QUESTION OF PICK'S CIRCUMSCRIBED CORTICAL ATROPHY (PICK'S DISEASE). K. ONARI and H. SPATZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:470 (Feb.) 1926.

Arnold Pick first described the symptom-complex which bears his name: a localized atrophy of the brain which he considered due to hemorrhage or softening. Stertz, however, demonstrated that there are striking differences which serve to differentiate Pick's type of atrophy from arteriosclerotic softening in the same area. Stertz, and also Gans, showed that the course and termination of this localized atrophy were sufficiently striking to be of great differential value. The etiology of the process remains unsolved. Pick believed that in a diffuse process, a seniie involution, a localized intensification of the process could occur producing focal symptoms, similar to those in Lissauer's type of general paralysis. In the latter, however, one has an accentuation of a diffuse paralytic process, whereas in Pick's atrophy the diffuse process may be more intense than the localized pathologic changes. The disease affects the frontal and temporal lobes in particular, and shows a special predilection for certain fibers while others escape. Careful investigations of cases of Pick's disease are not rare. In a case of atrophy of the frontal lobe, Gans tried to determine exactly the progress of the changes. He found a relation neither to the distribution of a vessel nor to a myelogenetic region, but determined that the process was related to one of Brodmann's cyto-architectonic areas. "The severely atrophied region corresponded to the regio frontalis (Brodmann)." This observation at least established that such areas have a functional as well as an architectonic capacity, and may be of some significance in diseases of the endogenous system. Etiologically, Gans, like Pick, assumed a relationship with the older involution process.

Onari and Spatz report a case of Pick's atrophy which was described first by Kraepelin and later by Stertz. The brain weighed 960 Gm. The convolutions were small over the entire cerebral surface, with yawning sulci. The process was much more marked in both temporal lobes, however, which showed a marked circumscribed atrophy which was an intensified type of the general atrophy over the entire brain. The atrophy did not involve the temporal lobes in their entirety. Heschel's convolutions and the posterior part of the first temporal convolution on one side, and Ammon's horn and the gyrus dentatus on the other were atrophied only slightly. The most extreme atrophy, however, was limited to the middle portion of the lobes; namely, the lower part of the first convolution and the second and third convolutions, as well as the gyrus fusiformis and hippocampi. The atrophy reached a particularly extreme grade in the temporal pole. In the frontal portions it was more noticeable than in the posterior parts. Microscopically, the right temporal lobe showed the gyrus dentatus and the cornu ammonis to be normal. The entire change lay in the medial portions of the temporal lobes, involving the gyrus hippocampi, the gyrus fusiformis, the second and third temporal gyri and the medial and lower parts of the first temporal gyrus. The outstanding change under low power consisted of a poor differentiation because of the loss of cells, with a more intensive staining of the white matter, thus making differentiation from the gray substance more difficult. Weigert preparations showed likewise a

more severe involvement of the middle portions of the temporal lobe. In these areas there was a marked loss of nerve cells, with the most extreme grade in the gyrus fusiformis. The most severe loss of cells was found in the upper cortical layers, the second and the upper portion of the third. In these areas the architecture was so disturbed as to render impossible a differentiation between layers 1, 2 and 3. In contrast to these, layer 4 was intact. The temporal pole likewise showed severe architectural changes which affected the upper more markedly than the lower layers. Examination of the nerve cells remaining in the affected areas showed that they were markedly shrunken and their pigment was increased. Bielschowsky stains showed: entire absence of plaques, the absence of Alzheimer's fibrillary changes, the lack of Alzheimer's argentophilic globules, and a severe disappearance of extracellular fibrils. This disappearance was more marked in the upper than in the lower layers (1 to 3*a*). The glia elements were increased in the affected areas without evidence of fresh proliferation. The glia cells contained much lipoid material. The vessels showed little of importance. The small vessels showed a swollen intima and adventitia, while the large vessels showed a cell-poor and fiber-rich adventitia. In addition to the temporal lobe changes, the island of Reil showed definite atrophic changes similar to those described above, but less severe. The basal ganglia showed complicated characteristics, with decrease in size of the caudate and loss of the smaller cells. The putamen was less severely involved.

The second case, one mentioned by Alzheimer, is reported more briefly. As in the previous case it was one of atrophy of the temporal lobe. In this case also only the middle convolutional regions of the temporal lobes were most severely atrophied (the second and third temporal convolutions and the gyrus fusiformis). The exterior portion of the temporal lobe, the first temporal gyrus and particularly the transverse gyri, the cornu ammonis and the gyrus dentatus were almost intact. One difference between this and the preceding case, however, is that in the second case the gyrus hippocampi was markedly atrophied and destroyed. The upper cortical layers (1 to 3*a*) were involved in the process. No arteriosclerotic changes were visible in the temporal areas. No plaques or fibrillary changes, as described by Alzheimer, were seen, but the argentophile bodies described by him were seen in the pyramidal cells.

The third case is one reported by Stertz, in which there was marked atrophy in both frontal lobes, the left possibly being more involved than the right. The convolutions over the rest of the brain were normal. In the left frontal area they were almost "microgyric." Not all of the frontal lobe, however, was equally affected. The orbital (gyrus rectus) and medial (gyrus fornicatus) portions and the first frontal gyrus were more severely injured. The region of the operculum also was involved markedly. As in the other cases the cortex was much reduced in size and the loss of cells occurred chiefly in the upper layers (1 to 3*a*).

The fourth case was one of Spielmeyer's in which both the frontal and the temporal regions were involved, with the rest of the brain intact. No relation was traceable to the blood supply. The loss of nerve cells was great and reached its highest degree in layer 3. Layers 1 and 2 showed changes; layer 4 was the best preserved of all the layers, while 5 and 6 often showed many cells lost. The cells remaining showed definite shrinking, while others were swollen, with excentric nuclei.

The fifth case was reported by Scholz from the clinic of Kraepelin and showed Pick's atrophy limited to the frontal lobe. The changes were similar to those described in the other cases, except that Scholz found much difficulty in differentiating these changes from those occurring postmortem. In this case there were diffuse and focal changes in the basal ganglia.

A discussion of the significance or etiology of Pick's disease must begin with a careful definition of what is meant by atrophy. Any more or less symmetrical diminution in the size of an organ is looked on as atrophy. It is an end-product which may be caused by many conditions, characterized chiefly by diminution in size. A further characteristic is the lack of qualitative deviation in the microscopic relationships (Recklinghausen). This conception of atrophy in its broader sense — diminution in size without gross destruction — is indispensable to neuropathology. The term atrophy, however, can be used in a narrower sense. The disease may be looked on as the end-result of a definite process. The morphologic characteristic of this specific "atrophying" process is to be found in the shrinkage of the nerve cell without change in structure, and this characteristic is important in differentiating the process from other regressive processes. Moreover, the "atrophying" process takes place with a slow tempo and a mild intensity. Onari and Spatz try to determine whether the atrophy in Pick's disease is the result of an inflammatory or a more or less acute degenerative process, or whether it is an atrophy in the narrower sense of the word. Atrophy may occur as a result of general paralysis or epidemic encephalitis in the later stages.

Alzheimer stressed the rôle of arteriosclerosis in the causation of atrophy. Against this possibility are several observations: In the cases described in this paper arteriosclerosis plays a minor rôle, no more sclerosis being present than in the average person of 50. This observation is corroborated by the reports of Pick, Gans, Rosenfeld, Fischer et al. Moreover, in the cases studied none of the macroscopic changes seen in arteriosclerosis (hemorrhages, softenings) have been present. The microscopic changes in the vessels of the case reported and the perivascular gliosis are mild in degree and can have no connection with the temporal lobe atrophy. The type of atrophy also speaks against arteriosclerosis or a vascular origin of any kind. Two possibilities, however, are present: (1) a lesion in a large basilar vessel during its course in the membranes; (2) disease of a small vessel within the brain substance. The symmetry of the process in Pick's atrophy is contrary to any such assumption. The important argument against it is the fact that the atrophy is confined to the middle portions of the temporal lobes, which correspond to no definite vascular distribution. In addition, the microscopic changes are not those due to disease of the smaller vessels and, in short, one can say that the distribution of the changes is in no way dependent on blood vessels. Pick's atrophy is a slow, insidiously progressive process, and is therefore an atrophy in the narrower sense, the most characteristic example of which is senile involution which has been held responsible by Pick for the process.

In senile brains Redlich-Fischer plaques and Alzheimer's neurofibrillary changes are present. These changes are so frequent, especially the former, that they are practically specific for senile involution. In the cases here studied, there have been no plaques or fibrillary changes either in the loci of severest atrophy or elsewhere. Moreover, the argentophilic bodies of Alzheimer have not been present characteristically. Does their absence preclude the possibility of a senile change? Not necessarily, for senile changes occur in a general way all through the body without any accentuation. The fact that in senile brains these changes do not occur is a good reason for not calling them senile, for while brown atrophy of the heart occurs in senile involution, the pathologist when given such an isolated heart is unable to say whether it is senile or is due to one of several other possibilities; e. g., cachexia or chronic infections. It is therefore possible to say that Pick's thesis, that his circumscribed cortical atrophy is caused by a localized senile process, can be confirmed by anatomic

observations but cannot be proved. The anatomy in itself does not preclude other possibilities.

Gans postulated that the atrophy involved a definite functional system and that Pick's disease was therefore one of the hereditary degenerative diseases. Does Pick's disease follow any definite system? In the cases of atrophy of the frontal lobe, the process passes beyond any such limit, while in atrophy of the temporal lobe it is most intense in the middle portions, not only in the author's cases, but in those of Pick, Gans, Rosenfeld and others. It is to be noted, therefore, that the relation to one of the primary regions of Brodmann is only approximate. From the point of view of development, the temporal lobe has many peculiarities. The medioventral portion belongs phylogenetically to the oldest parts of the end-brain. As for the rest, according to Kappers, the first temporal convolution with the gyrus transversus is the oldest part. If this view of Kappers is accepted, only a middle portion of the temporal lobe remains to be accounted for genetically. This portion is present in lower animals but is first particularly developed and differentiated in higher animals; it is therefore of more recent development phylogenetically, and is most developed in man. Kappers believes that it develops with the temporopontile tracts. One can say, then, that "the atrophying process has its center in a genetically recent center." In the portions of the temporal lobe that escape are the hearing and smell centers, while the portions involved have less well known functions and are probably more highly developed. The localization of the process in the upper cortical layers also points to a functional process, the upper layers being concerned with associative processes, the lower giving rise to the projection fibers. The distribution of Pick's atrophy is not selective. In a series of cases it had noteworthy relations to technic, genetic and functional systems.

ALPERS, Philadelphia.

SUBARACHNOID BLOCK, PARTICULARLY OF THE CEREBELLOMEDULLARY CISTERN. JOHANNES ZANGE, München. med. Wchnschr. **73**:1150 (July) 1926.

Subarachnoid block is a break in the cerebrospinal fluid system in which certain of its main branches are shut off from one another. A block may occur: (1) in the spinal subarachnoid space (spinal block); (2) in the region of the foramen magnum (cisternal block); (3) in the region of the foramen of Magendie and the fourth ventricle (cerebral block). A block may be due to a variety of causes; it may be caused by infectious products, by adhesions and deformities, or by crowding of the brain by tumor masses, etc. In the spinal block, in addition to the causes mentioned, so-called compression of the spinal cord due to tumor, displacement of vertebrae, vertebral injuries, etc., must be considered. In cisternal block, the crowding in of cerebellar parts or pressure due to tumor masses enters into the picture, and in cerebral block displacement due to tumor masses, especially in the cerebellopontile angle, may be the cause. If a cisternal block is not recognized, grave errors in diagnosis and in prognosis may be made, especialy if the block is in the brain and lumbar puncture is relied on for diagnosis.

The author and Dr. Kindler have done a great deal of work in regard to the treatment of cisternal block, and in this article give a report of their results. Cisternal block occurs more frequently than is usually supposed. In the last two years ten cases have been observed in the author's clinic. Six were diagnosed clinically and four post mortem, as follows: cerebellar tumors three; pachymeningitis hemorrhagica interna one; pyocephalus interior following bacterial emboli of the choroid plexus one; otogenous cerebellar abscesses three; otogenous basal meningitis two.

Inflammatory processes may cause blocking of the subarachnoid space in the region of the cisterna magna and elsewhere. However, such a condition would not exist without edema of the brain, the formation of tumors, increase in pressure and other similar conditions. The brain is heavier than the fluid and will sink to the floor of the skull if conditions do not exist to prevent it from doing so; but it is supported by the spinal fluid pressure and is suspended in the fluid. Even with increased volume and increased pressure, the brain remains suspended as long as the central nervous system continues to be surrounded by fluid. No matter how much the pressure is increased, it increases in the same proportions on all sides; the specific weight of the brain in tumors and edema does not increase to such an extent as to cause tearing of the membranes. It is only when the fluid no longer encircles the central nervous system that the brain drops to the floor of the skull, and it is then that tumor parts, under the influence of increased pressure, are forced into the cistern and by crowding the medulla cause transverse blocking of the entire subarachnoid space. This explains why a cisternal block occurs only in some cases in which there is a process that narrows the space either at the time of a spinal puncture or of gradual development without outside interference. In two of the author's cases there was gradual blocking of the cistern, the symptoms at first being incomplete and later complete. In one of these cases there was gradual blocking with subsequent disappearance of symptoms.

When blocking is discovered at puncture, the fluid that has been withdrawn or a corresponding amount of physiologic sodium chloride solution or of Ringer's solution should be allowed to flow back into the spinal sac, or the head should be lowered and a somewhat larger amount of fluid inserted under moderate pressure.

The clinical diagnosis of cisternal block is determined by dry puncture; that is, when no fluid is obtained on cisternal puncture even if jugular pressure (Queckenstedt test) is made. In incomplete block, when the needle enters the cistern some fluid flows out, but with the Queckenstedt test no increase in pressure is noted in the spinal fluid, or only a small, sluggish one. As a further aid in the diagnosis of cisternal block the following symptoms may be observed at times: an unusually rapid decrease of the fluid pressure during the drawing off of fluid by lumbar puncture; the existence of pronounced symptoms of brain pressure with unusually rapid decrease of pressure, and the slowing or discontinuance of pulsation of the fluid in the manometer. These symptoms are not pathognomonic of cisternal block alone but may be applied generally to any subarachnoid block.

The author advises the use of a large needle similar to that employed in the Nisser brain puncture, for cistern puncture when block is present. (He even suggests the possible advisability of obtaining a cylinder of tissue in this manner which may be examined histologically.)

The clinical significance of cisternal block, especially in inflammatory diseases of the brain, is great. The serious injury that may be done if a block is overlooked and spinal puncture relied on for diagnosis is shown by four cases from the author's series:

Case 1: Otogenous meningitis following mastoid disease; 4,000 cells in the spinal fluid, no bacteria; rise of temperature; severe headache; stiffness of neck, etc. After operation on the mastoid and middle ear, the condition returned to normal with an increase of cells in the fluid first to 3,000, then to 1,600. In spite of the apparent recovery, death occurred suddenly from respiratory

failure. Postmortem examination showed large subdural and subarachnoid abscess in the region of the foramen magnum with displacement of the medulla oblongata.

Case 2: Otogenous cerebellar abscess with cholesteatoma and infection of the middle ear. Before operation there was headache but no fever. The spinal fluid was normal except for moderate increase of pressure. After operation the headaches continued; there was no fever, and the spinal fluid was normal. Death was due to respiratory paralysis. Postmortem examination revealed a subdural abscess, the size of a walnut, in the posterior cranial fossa, with displacement of the cerebellum.

Case 3: Cerebellar abscess following cholesteatoma and infection, with meningitis. Before operation there were 1,450 cells in the spinal fluid. Radical operation was performed and the cerebellar abscess opened. Four days later there was only 1 leukocyte in the fluid. Seven days later there were 85 leukocytes. Necropsy indicated pyocephalus internus and basal meningitis (incomplete block).

Case 4: Meningitis following a war wound. In spite of symptoms of marked increase of brain pressure and fever, there was noticeable improvement in the spinal fluid observations. There was a falling off of from 5,333 to 2,107 and finally to 1,000 in the cell count in the spinal fluid during the three days before death. Necropsy revealed pyocephalus internus following bacterial emboli of the choroid plexus with edema of the brain.

MOERSCH, Rochester, Minn.

THE PIGMENTED MOLES AND NERVE TUMORS. MASSON, Ann. d'anat. path. et d'anat. norm. médico-chir. **3**:417; **3**:657, 1926.

The innumerable researches on pigmented moles have not yet demonstrated their origin, although several theories have been advanced. The principal ones are that they arise from endothelial elements, from proliferation of chromatophores, from connective tissue and from epithelial tissue. The pigment, which is a melanin, arises in certain multipolar cells of the epiderm known as the cells of Langerhans. By staining sections with "dopa" (dioxyphenylalamine), Bloch has shown all the cells of Langerhans to be potentially melanoblastic. However, there are certain cells in the dermis that also contain pigment granules. These are in no sense epithelial, but rather histocytes of the reticulo-endothelial system that have taken up the pigment granules by phagocytosis. These are chromatophores. On previous occasions, the author has considered that the melanotic tumors of the skin appear as a result of proliferation of the cells of Langerhans, but when he reviewed the subject, the deep cells of the mole appeared to him more like the cells of the sheath of Schwann than fibroblasts. "Pursuing my studies, I was forced to recognize the constancy of the metaplasia (of these Schwann cells), the frequency of myoid cells and the absence of connective tissue metaplasia, and was brought to a complete modification of the conception of moles as brought forward in my report. And at the end, I foresaw that that conception would give way to another, purely nervous, applicable not only to moles and nevocancers, but also to all melanomas."

Soldan had already advanced this view, in 1899, in a masterpiece of pathologic litrature against the "menacing veto" of Unna. By using Weigert's stain, he saw myelinated nerve fibers lose themselves among the masses of cells of the pigmented mole. Moreover, he brought all the tumors of the nerves into direct relationship with these cutaneous tumors.

The most favorable moles for study are those of the scalp. The cutaneous elements appear relatively normal, but more widely spaced than normal as if separated by the mass of tumor tissue. Indeed, the sebaceous glands and hair follicles found on a pedunculated tumor would practically cover the width of the pedicle. At the sides of the tumor the hairs are directed in an oblique direction as though forcibly separated. At the base of the tumor are numerous myelinated nerve fibers that send branches up into the mass. These nerve fibers are better studied by methods of silver impregnation, and Masson has used his favorite trichrome stain, ferric hematoxylin, acid fuchsin and aniline blue. Several colored plates and numerous drawings illustrate the long article.

When specially stained, the nerve fibers arising in the underlying cutaneous nerves are found ramifying and anastomosing, running upward to lose themselves among the cells of the nevus. A number of ovoid bodies made up of numerous sheaves bound together by fine fibers are inlaid in the tumor. These greatly resemble the corpuscles of Meissner, although they are known as the corpuscles of the mole. The fiber, after spiraling around the corpuscle, seems to end within it. These bodies become more and more numerous as the surface is approached.

The epithelioid cells found within the dermis are massed in the deeper parts in close relation with the corpuscles of the nevus, where they seem to form the sheath, but they spread out more as they approach the surface until they lie singly just beneath the epidermis. The nevic fibers arising from the trunks below lose themselves among these epithelioid cells. The cells, although generally rounded, appear to have several prolongations of delicate caliber which bring them into continuity with the neuroid fibers attached to deeper trunks. Those epithelioid cells that are found in the epidermis appear to be homologous with the tactile cells of Merkel-Ranvier. Careful study shows, moreover, that these tactile cells, the clear cells of normal epidermis and of the mole, are all identical.

"The moles of the scalp are tumors due to the proliferation of a number of elements of nervous origin, bound to myelinated nerves, associated in a plexiform mass, and capable of being differentiated into satellite cells characteristic of tactile terminations, especially under the form of the corpuscles of Meissner and the cells of Merkel-Ranvier."

The pigment of these moles, then, is of secondary importance. By special methods the pigment capacity of the cells can be determined, and it is found that the cells of Langerhans, the hyaloid cells and those of Merkel-Ranvier are morphologic variants of the same original type of cell.

The pigment-bearing function of the skin belongs, therefore, to the same cells, portions of the sensory nervous system, that form the corpuscles of Meissner and the tactile cells of Merkel-Ranvier. Masson therefore wishes to term these pigmented moles neuronevi.

In regard to the study of moles from other parts of the body, those of children or of recent appearance are the best for study. The nerve fibers in them are much more numerous than in normal skin, even though it is safe to say that many of these do not take the silver stain. The cellular moles are therefore tumors resulting from the proliferation of the neurites and the peripheral neuroglia or sheaths of Schwann.

In the study of the early tumors, however, the epidermis seems to be involved coincidently with the dermis, and a double origin seems probable. This rests on the fact that the cells of Langerhans play such an important part in the formation of the mole. These cells, if they really arise from the epidermis, do so at an early stage in intra-uterine life. Moreover, several related facts

show clearly that these cells are closely allied to the epidermic terminations of nerve fibers, and indeed are themselves derivatives of the nervous system.

FREEMAN, Washington, D. C.

THE DEVELOPMENT OF MOTILITY AND BEHAVIOR REACTIONS IN THE TOADFISH (OPSANUS TAU). HENRY CARROLL TRACY, J. Comp. Neurol. **40**:254 (April 15) 1926.

For more than twenty years, Coghill has been publishing (chiefly in the *Journal of Comparative Neurology*) a remarkable series of observations on the development of the behavior pattern of the salamander *Amblystoma*. This most ambitious of several similar programs involves the exact determination of the larva's first reactions to stimulation and then the steps in the complication of the behavior up to free-swimming and feeding stages. Following this, the individually tested larvae of known physiologic age are examined histologically in order to learn the changes in structural organization at each step in the development of the behavior pattern.

Tracy has followed substantially the same procedure in his studies of the development of the behavior pattern of the toadfish *Opsanus*. This first paper, a memoir of 118 pages, describes only the physiologic observations. The histologic reports will follow.

The salamander is hatched in an immature condition, and in adaptation to the requirements of life in the open it develops enteroceptive reflexes early, in advance of most of the visceral reflexes. The toadfish, on the other hand, has a large yolk by which it is nourished for a long time before hatching. The eggs hatch in about three weeks, and they remain firmly attached for about three weeks after hatching. Visceral reflexes and automatisms and complex spontaneous movements are elaborately developed before exteroceptive reactions appear. The comparison of the two developmental patterns is therefore instructive.

The first observable movement is the heart beat, which was carefully studied. Spontaneous branchial movements appear soon after hatching. However, long before hatching there are various spontaneous movements of the body which are internally excited (endogenous). These continue into the free-swimming stages. They appear before the exteroceptive nervous system is functional and are modified but not abolished by the functional maturity of the latter system. In an unchanging environment, the impulse to progression is of intrinsic origin; orientation results from external stimulation, but this does not begin to appear until after hatching. The primitive neuromuscular mechanism of progression is organized for endogenous movements, and this organization determines the general character and pattern of the responses, even in later stages when exteroceptive stimuli are effective. External stimuli do not "cause" the reaction; they merely condition it by determining its orientation, its incidence in time and perhaps its intensity. They activate the same mechanisms as intrinsic stimuli, but responses oriented to specific parts of the environment result by producing an asymmetrical tonus of the lateral musculature.

The development of cutaneous reflexes was studied in detail, and the relation of these to spontaneous movement investigated. Proprioceptive reactions are absent in newly hatched larvae and make their appearance after the tactile reactions. Considerable attention was devoted to the development of reactions to rotation. The sequence is as follows: (1) slow phase of nystagmus during rotation — slow roll of eyes back to resting position on stopping rotation;

(2) compensatory coil of the body; (3) back-stroke of the body on stopping rotation — eye comes to rest by a series of oscillations; (4) quick phase of nystagmus; (5) active swimming opposite to direction of rotation (young adults).

Reactions to different types of external stimuli develop in the toadfish larva in the following order: tactile, vibratory, proprioceptive, rotation and light. Tactile responses of the skin develop at different rates in different regions.

The paper closes with a valuable general discussion of the relations of endogenous and exogenous behavior. The first of these two components of behavior constitutes the fundamental feature of the motility of the body (progression), and is conditioned by internal physiologic adjustments in connection with metabolism. Exogenous activity is oriented activity; it appears to be essentially the modification of the endogenous activity which results either from the stimuli which the organism meets during its excursions in the environment, or from those aroused by changes in the external relations of energy. The segmental reflex is not primary, but is the last type of activity to develop, and it does not involve progression movements. It is therefore probably dependent on specialized mechanisms differentiated from the primitive motor pathway.

The spontaneous movements of the embryo pass by insensible transitional stages into the so-called voluntary movements of the adult. Voluntary movement is the activity of the organism which results from the integration of the spontaneous activity of an indeterminate number of individual reaction systems (visceral and associational) of which the body is composed.

HERRICK, Chicago.

TYPES OF NEUROSYPHILIS IN RELATION TO TREATMENT. HENRY A. BUNKER, JR., J. A. M. A. **86**:1815 (June 12) 1926.

The author calls attention to the variation in amenability to treatment of syphilis between the case in which the spinal fluid readily becomes negative after treatment and the case intractable to ordinary methods of treatment and which develops sooner or later into tabes or general paralysis. Formerly this made little difference, as the intractable case was hopeless while the more tractable types could be treated by ordinary intravenous therapy. Now, however, with intraspinal therapy, tryparsamide and the malarial treatment, it is hightly important to identify these formerly intractable cases at the outset in order to determine the proper treatment. Bunker immediately dispenses with attempts to distinguish between the meningovascular and parenchymatous forms of neurosyphilis and then calls attention to the fact that the symptoms are of no great help, the same symptoms occurring in both types due, he believes, to the fact that a meningitis (Dunlap), perhaps different in details, exists in both types. Similarly, the spinal fluid examinations are of little value in type determination. In general a Wassermann reaction, negative with 0.2 cc. and particularly with 0.5 cc., is against the diagnosis of general paralysis in untreated patients, but the converse is not necessarily true. Many cases of tabes show weakly positive or even negative reactions. A nonparalytic colloidal gold curve is against general paralysis but a paralytic type does not necessarily mean paralysis rather than the meningovascular form. Clinical differentiation then is difficult, sometimes impossible and is not needful as other means can be used.

The important thing is repeated spinal fluid examination, the need for which Bunker emphasizes by four case reports. In case 1, the patient was committed

seven years after the initial chancre for which he received rather intensive intravenous treatment and for which he had had two lumbar punctures. There had been symptomatic amelioration. He should have had a third puncture which would have shown the slight effect of the treatment in the spinal fluid. This case also shows how misleading and of how little value relief of symptoms is in the absence of improvement in the spinal fluid readings, and that the symptomatic improvement is followed by relapse and commitment. Case 2 is that of a patient in whom the diagnosis of neurosyphilis was made by spinal fluid examination fifteen months after the discovery of highly suggestive neurologic signs; the man was known to have contracted syphilis seven years previously, and when treatment was resumed he was on the verge of commitment for paralysis. Case 3 was well handled as far as the patient made it possible (he refused Swift-Ellis treatment after one course). This case calls for the adoption of one or more of the four following procedures: continuation of the Swift-Ellis technic at shorter intervals (it had been three weeks); supplementing it with intracisternal injections; a thorough trial of tryparsamide, and treatment with malaria. Bunker believes that patients who present strongly persistent spinal fluid readings after a thorough trial of intravenous administration of arsphenamine should be given the malaria treatment which affects the underlying disease considerably although its effect on the fluid is either slight or very gradual. Case 4 is one of unconsciousness two years after a chancre, with many hundred cells in the spinal fluid and a positive Wassermann reaction. Three years later, there were Argyll Robertson pupils, diminished patellar reflexes, ataxia, speech defect, tremor of circumoral muscles, and some memory defect. A course of intravenous arsphenamine produced improvement in memory. This case is a present problem and not like the other one of omniscience of "hindsight."

We cannot, then, escape the deduction that our all important consideration must be whether or not treatment is accomplishing the purpose intended, regardless of the classification of the case from a clinical or pathologic standpoint. Bunker recommends that a patient with neurosyphilis should receive twelve weekly injections of arsphenamine or neo-arsphenamine. A spinal fluid examination should then be made to discover the effect of this treatment. Some cases will clear up entirely or give promise of doing so under further systemic treatment. Others will show some modification in the fluid, and we must decide whether to give more intravenous arsphenamine or intraspinal treatments or several courses of tryparsamide. Repeated spinal fluid examinations are here imperative. In the cases that show no change in the fluid whatever, there is reason to believe that two weeks given over to the malaria treatment may be worth several months of the intraspinal or tryparsamide therapy.

CHAMBERS, Syracuse, N. Y.

GENERAL PARALYSIS WITH SLOW COURSE. T. SCHMIDT-KRAEPELIN, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:564 (Feb.) 1926.

"Among the numerous cases of general paralysis reported by various authors in the course of recent years, cases with an abnormally protracted course, there are not more than a dozen in which the diagnosis of general paresis could be corroborated histologically in the sense of 'cured' general paresis of Hoche, Spielmeyer et al." Among the cases with an extremely slow course, about two-thirds show the picture of stationary general paralysis, while in only two could one see a "cured" general paralysis. The number of anatomically certain cases of stationary and "cured" general paralysis is still so small that it is worth while analyzing a large group of cases to study the incidence of the

slow ones. It was possible to survey 2,300 cases from the clinic at Munich, in 2,100 of which there were complete records. The cases selected from this material were those that ran a course of six years from the beginning of the first psychic symptoms to the time of death. Of 144 cases so selected eighty-nine showed the typical characteristics of general paralysis; eight showed only a pleocytosis in the spinal fluid; thirteen, only a positive Wassermann reaction with the blood; in twenty-eight examination was not made, and six were serologically negative. Cases were included which did not appear to be general paralysis, but which showed general paralytic blood and spinal fluid characteristics. Chief stress was placed on the differences between cases with a prolonged course and cases with the usual course. About 1,950 cases, records of which were collected by Kraepelin, from 1905 to 1921 were used as controls.

The conclusions arrived at by Schmidt-Kraepelin after a thorough statistical study may be summarized as follows: 1. The proportion with a course of more than six years amounts to about 6.8 per cent. The percentage with a course of more than six years is 3 per cent and more than eight years, 3.8 per cent. 2. The number of women who have protracted cases of general paralysis is greater than the number who have cases that follow the usual course. 3. True taboparesis, preparalytic organic nervous disturbances on a basis of cerebral syphilis and isolated epileptic attacks of long duration are more common in the protracted than in the usual general paralysis. Changes in temperament, such as nervous irritability, attacks of anger and emotional instability, are more common in the protracted cases. 4. Neither the time of infection nor the length of the incubation period has any noticeable influence on the duration of the general paralytic process. On the other hand, the duration and the incubation period show a certain shortening with increasing age of the time of infection. About three times as many patients were infected before 30 as after 30 years of age. 5. Specific treatment either before or after the outbreak of general paralysis has no influence on the duration of the process. Febrile diseases of many sorts occurred during the course of these extremely slow, progressive cases; among them articular rheumatism and typhus were most frequent; tuberculosis, psoriasis, malaria and scarlet fever were also observed. In the protracted cases in which a febrile process occurred, the disease was much more benign. Men semed to be more affected by the fevers than women. 6. The occurrence of tabes and cerebral syphilis in conjunction with psychogenic or psychotic disturbances of varied origin (hysteria, mania, depression, delirium tremens, dementia paranoides, Korsakoff psychosis, arteriosclerosis, senile dementia) produces clinical pictures whose differentiation from typical general paralysis is often extremely difficult. 7. Circular and depressive forms are more common in cases with a slow course. Katatonic and paranoid manifestations, as well as hallucinations, occur more commonly than in the cases of ordinary duration. 8. Delirious states and visual hallucinations are more common in alcoholic persons with general paralysis than in non-alcoholic persons. 9. Alcoholism in the protracted cases of general paralysis is about as common in women as in men. 10. Symptoms of dorsal column involvement are common and often occur with spastic phenomena. 11. In about 75 per cent of the protracted cases epileptic attacks occur, especially in demented patients. In the beginning of the disease, general epileptic attacks are more frequent, while in the later stages epilepsy of jacksonian type is more common. 12. Remissions occur often in protracted cases, especially in the beginning of the disease. They are especially common in alcoholic persons, but occur most frequently in the circular and agitated forms.

ALPERS, Philadelphia.

ANATOMY OF THE SYMPATHETIC NERVOUS SYSTEM WITH REFERENCE TO SYMPATHECTOMY AND RAMISECTION. S. W. RANSON, J. A. M. A. **86**:1886 (June 19) 1926.

Before proceeding to discuss the surgery of the sympathetic nervous system, Ranson presents a masterly description of the anatomy of this system with diagrams. Cervical sympathectomy for the relief of angina has awakened a new interest in the sensory fibers of the heart. This seems readily explicable, because the direction of radiation of the pain indicates that the fibers concerned reach the sympathetic system through the white rami of the upper three left thoracic nerves. The work of Coffey and Brown on the superior cervical ganglion seems to make such a simple explanation untenable. However, histologic, physiologic and clinical evidence makes it almost certain that high cervical sympathectomy leaves the afferent cardiac fibers uninjured.

Ranson and Edgeworth have shown that the large sensory fibers in the cardiac plexus of the dog and cat come from the vagus and the upper three thoracic nerves, and thence through the white rami to the inferior and middle cervical ganglia and the nerves passing therefrom to the heart. There are no large sensory fibers above the middle cervical ganglion. Specimens removed from patients at operation lead us to believe that the sensory pathways in man are essentially the same as those in the dog and cat.

Physiologic and clinical evidence also supports this view. Anginal pain is referred to the cutaneous distribution of the first three left thoracic nerves. Jonnesco and Jonnesen recently showed, in operations for angina under local anesthesia, that stimulation of the upper cervical sympathetic trunk, the upper connection between the vagus and the upper sympathetic trunk having been severed, produced no pain or reflex response while stimulation of the nerves from the inferior cervical ganglion and the annulus of Vieussens caused pain and reflex changes in respiratory rhythm. Severe pain in the left arm resulted from avulsion of the first thoracic ganglion. Schittenhelm and Kappis injected procaine hydrochloride into the upper sympathetic trunk without result, but the pain disappeared on injection of the lower part. Vagal injection gave no relief.

Ranson states that anatomy offers no explanation for the relief of anginal pain following resection of the superior cervical ganglion, but offers a possible although, as he says, a highly improbable pathway. The afferent impulses which reach the brain from the vagus do not cause pain but rather produce reflexes, such as lowering of blood pressure. Section of the depressor branch of the vagus for relief of angina pectoris has been advocated, but in many if not in most cases there is no well defined depressor nerve in man. Ranson mentions the work of Royle and Hunter, directing attention to the possible maintenance of tonus of skeletal muscle by the sympathetic system, but the observations of Hinsey and Ranson's work on cats leads him to conclude that the sympathetic system is not responsible for the exaggeration of tonus of skeletal muscles following decerebration or for that caused by tetanus toxin.

No attempts have been made to interfere with the craniosacral autonomic (parasympathetic) system, but section or even blocking of the splanchnic nerves offers attractive possibilities.

Periarterial sympathectomy has caused renewed interest in the innervation of the blood vessels, but the results seem to indicate that the vasoconstrictor and sensory fibers for the peripheral vessels accompany the main arterial trunks into the limbs, and this is in conflict with all that is known regarding the innervation of the blood vessels. An explanation of this innervation is presented with a diagram (Leriche).

Despite Leriche's assumption that the constrictor fibers for the cutaneous blood vessels take a course analogous to the splanchnic vessels, Ranson believes with Kramer and Todd that there is no fundamental difference between man and laboratory animals and that the constrictor fibers accompany the spinal nerves, very few accompanying the larger arteries for any distance toward the periphery.

No satisfactory explanation has then been found for the hyperemia following periarterial sympathectomy nor for the relief of pain afforded some patients thereby. The blood vessels possess sensory fibers, but these run centrally in the spinal nerves. Ranson suggests that the relief from pain may depend on the hyperemia and resultant improved peripheral nutrition.

CHAMBERS, Syracuse, N. Y.

CLINICAL AND HISTOLOGIC CONTRIBUTIONS TO CHRONIC SYPHILIS OF THE CENTRAL NERVOUS SYSTEM WITH PARTICULAR REFERENCE TO VASCULAR SYPHILIS. ROBUSTOW, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:757 (June) 1926.

This is a discussion of eight cases of syphilitic disease of the central nervous system, with at times uncommon manifestations, and at others an atypical general paralysis causing great difficulties in differential diagnosis. The first case occurred in a man, aged 50, who had had a gonorrheal infection about twenty years previously; he first developed nervous manifestations, such as depression and quietness, which were attributed to chronic alcoholism because of an alcoholic history with negative serologic and objective neurologic characteristics. This was followed by disturbance in gait, confusion and urinary and rectal incontinence. The left pupil was larger than the right; the tongue deviated to the left, and there was moderately increased tone in all four extremities with bilateral ankle clonus and at times a Babinski sign on the left. There was a positive Romberg sign. The patient was disoriented and was unable to understand complicated questions. The blood Wassermann test was weakly positive. The spinal fluid showed 15 cells, a positive Wassermann reaction and an atypical general paralytic or meningitic curve. Anatomically, there was gummatous meningitis at the base, with a gumma in the left temporal lobe and diffuse meningitis over the cerebrum and cerebellum. Microscopic examination showed a general gummatous meningitis and a gumma in the temporal lobe. The pial vessels showed massive intimal infiltration and proliferation of a hyperplastic nature. The question is raised whether the vascular changes were syphilitic or arteriosclerotic in origin. Pathologists look on arteriosclerosis as a hyperplastic and degenerative process of varied causation. Robustow thinks the process is syphilitic in this case because of the proliferation without fatty degeneration or necrosis. In ordinary arteriosclerosis, in addition to the hyperplasia there is degeneration, whereas in syphilitic vascular disease there is proliferation, and the regressive changes are exceptional.

In case 2 the diagnosis was chronic cerebral syphilis with dementia; chronic syphilitic vascular disease with foci in the central nervous system. At 19, the patient developed gradual paralysis of the left side which remained constant, headaches on the left side occurring later. Objectively, the man showed unequal pupils, one of which reacted poorly to light, left spastic hemiparesis with ankle clonus but no Babinski sign, and dementia. The blood and spinal fluid were normal on several occasions. The pia showed marked intimal proliferation of the vessels without degenerative changes. Robustow says this is due to syphilis. Syphilitic aortitis was present. In case 3, the diagnosis was cerebral syphilis

or atypical general paralysis. The patient had hemiplegia with aphasia, positive Wassermann reactions with the blood and spinal fluid, and twelve cells in the latter. The aphasia cleared up but the hemiplegia was progressive, and the patient became depressed, apathetic and excitable. She was removed from the hospital but returned later with hemiparesis still present; she had dysarthria and was unable to stand or walk without support. The blood Wassermann reaction was negative; there were 84 cells and a positive Wassermann reaction in the spinal fluid. Autopsy showed syphilitic vascular disease of the brain in the larger vessels, with intimal proliferation and syphilitic endarteritis of the small vessels. In case 4 the diagnosis was tertiary syphilis, mild meningitis, arteriosclerosis of the basilar and pial vessels with secondary parenchymatous disturbances. In this case there were marked gummatous changes in the skull, but the vascular changes were in the nature of arteriosclerosis. There was a mild syphilitic meningitis. In case 5 the diagnosis was cerebral syphilis or general paralysis. This patient had an apoplectic attack. He had irregular, unequal pupils, left hemiparesis with a Babinski sign, confusion and excitability with confabulation. The blood Wassermann test was strongly positive. A spinal fluid Wassermann test made later was positive with 1 cc. of fluid. Necropsy showed vessel changes in the pial and basilar vessels with intimal proliferation. Case 6 was similar, of long-standing cerebral syphilis with apoplectic onset. The vascular changes were similar to those in case 5. The other two cases showed similar changes.

ALPERS, Philadelphia.

ARTERIOSCLEROSIS AND INCREASED BLOOD PRESSURE. EXPERIMENTAL PRODUCTION. FRANKLIN R. NUZUM; BEATRICE SEEGAL; RUTH GARLAND and MARGARET OSBORNE, Arch. Int. Med. **37**:735 (June) 1926.

The authors conducted a series of experiments on rabbits fed a high protein diet. Three groups of twelve animals each were observed during periods ranging from three months to two years, with careful blood pressure readings and blood chemistry studies. The results were tabulated on graphic charts for each group, and the pathologic changes found at autopsy were carefully recorded.

The animals of group 1, which were fed on animal protein in the form of liver for from three to eleven months, presented evidence of extensive arteriosclerosis of the intimal type. There was no evidence of spontaneous (medial) sclerosis in any animal of this group. The blood pressures in this group were higher than in any other, and the readings were higher in those animals in which the sclerosis was most marked. There was also definite evidence of injury to the kidneys, and the urine was highly acid.

The animals of group 2, fed on meat protein for two years, showed marked arteriosclerosis, particularly in the aortas. Intimal degenerative changes were predominant, but three of the group showed spontaneous, or medial, sclerosis. The most marked changes were shown in the animals fed on this diet for the longest period. These animals showed also the highest blood pressures and the most marked evidence of injury to the kidneys.

The animals of group 3, fed on soy bean protein with the addition of some greens did not show true arteriosclerosis. Three of the group showed some spontaneous or medial sclerosis, which in one animal might have been traceable to intercurrent infection. The blood pressures in this group were not elevated, and the kidneys did not show evidence of injury. The blood chemistry studies showed no increase of nonprotein nitrogen or urea nitrogen.

The control group of twelve animals kept under the same living conditions on a normal diet for two years did not show any evidence of arteriosclerosis.

The authors have given a clear and comprehensive study of the histologic changes presented at autopsy. They traced the development of the degeneration, beginning with the small yellow specks in the intima, which are due to deposits of fat droplets containing cholesterin esters, on to the grosser lesions of the atheromatous plaques. The experiments proved conclusively that arteriosclerosis with increase in blood pressure can be produced in rabbits without an increase of cholesterol in the diet. They also showed that diet high in protein has the effect of disturbing the acid-base balance and results in the excretion of highly acid urine.

The practical significance of these experiments seems to be the analogy between the arteriosclerosis of rabbits and man, and the reasonable conclusion that the factors concerned in one are applicable to the other. The authors have given a clear and instructive picture of the etiology and pathology of experimental arteriosclerosis and have opened a wide path for future research along dietetic lines. The thought that arteriosclerosis in man is most often due to a high protein diet is not new, but the importance of this factor has never been more forcibly presented.

PLEASANTS, West Chester, Pa.

THE REGIONAL DISTRIBUTION OF ARTERIOSCLEROTIC CHANGES IN THE BRAIN. MAKOTO KODAMA, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:597 (May) 1926.

Alzheimer pointed out the varying distribution of the regional changes in cerebral arteriosclerosis. In 1902, he wrote: "It is a peculiarity of arteriosclerotic vascular disease that it does not involve all the vessels in the same degree, but reaches a particularly high grade now in one region, now in another. Sometimes the disease involves the vessels of the brain stem preferably (arteriosclerotic bulbar palsy), sometimes chiefly the long vessels of the white matter in the brain (Binswanger's encephalitis subcorticalis chronica diffusa), and sometimes the small cortical vessels." Spielmeyer also has been concerned with this problem, and has differentiated the gross form of cerebral arteriosclerosis involving the brain stem from the arteriosclerosis of the cerebral membranes. Systematic studies of the question of localization in cerebral arteriosclerosis are extremely few. Bucholz studied five cases with this point in mind, and found that the chief foci were in the white matter and to a less extent in the basal ganglia. Schob described a case of cerebral arteriosclerosis with changes in the pial and cortical vessels. Because of the lack of systematic studies of localization in cerebral arteriosclerosis, Kodama has taken for study eighteen cases from Spielmeyer's clinic, which were diagnosed both clinically and pathologically as cerebral arteriosclerosis, and has looked for evidences of regional changes in the pathologic condition. Of the arteriosclerotic changes found, the vessels of the brain stem were involved most often, more often than those of the meninges. Of the vessels in the cerebrum, those in the white matter were involved more often than those in the cortex. The actual involvement was: arteriosclerosis purely in the brain stem, four cases; in the cerebrum, three; arteriosclerosis chiefly in the brain stem, four, and in the cerebrum, none.

The most common site of arteriosclerosis in the basal ganglia is the putamen, after which comes the caudate nucleus, and last of all the globus pallidus. In the putamen, small foci are found in the head of the caudate nucleus, spreading out over the anterior limb of the internal capsule and the

anterior part of the putamen. This characteristic site of predilection was shown by Bucholz and also by Kashida. In only three cases was the internal capsule involved—twice in the middle of the anterior limb, and once in the lower part of the same region. In the cerebrum, the areas of softening were most common in the occipital lobes. Kodama found the most intense sclerosis in the basilar vessels and in the vessels of the putamen. The vessels in the globus pallidus were less markedly thickened than those in the putamen, but calcification was more common. Status cribratus occurred throughout the brain, but more especially in the putamen. The vessels of the white matter showed atheromatosis most frequently, while those of the cortex tended to fibrosis and sclerosis. Kodama agrees with Alzheimer and Spielmeyer that cerebral arteriosclerosis can be divided into two main types: that affecting the cerebrum particularly, and that affecting the basilar vessels. In the type involving the cerebrum, two types can be differentiated: one localized in the cortex, the other in the gray matter. In the cortex, besides the customary perivascular gliosis, are found the état vermoulu of Pierre Marie and the cortical moth-eaten appearance described by Alzheimer. Mixed cases of involvement of both the brain stem and the cerebrum are more common than the isolated cases and comprise 60 per cent of the total.

ALPERS, Philadelphia.

CONDITION OF THE CENTRAL NERVOUS SYSTEM IN TYPHUS. P. M. FELDMANN, Arch. f. Psychiat. u. Neurol. **77**:3 (June) 1926.

During the typhus epidemic in Russia the author studied the various neurologic complications occurring in the course of the disease. Within two years (1920 and 1921), fifty-five of the patients admitted to one of the hospitals showed definite neurologic conditions: twenty-eight hemiplegias, eighteen disseminate encephalitides, four diseased spinal cords, one acute hydrocephalus and four acute ataxias. It is important to note that the conditions enumerated are definite pathologic states of the central nervous system, and should not be confounded with symptoms, such as headache, delirium, sleeplessness, etc., which occur frequently in typhus and are more or less characteristic of the disease. The hemiplegias develop suddenly, as a rule, without apoplectic coma, and are probably due to vascular lesions. They arise either during the last few days of the febrile period or within the first few days after it. They seem to affect younger patients most frequently, which excludes an arteriosclerotic origin. No psychic and few sensory disturbances are associated with the hemiplegia. Although restorations are reported, the vast majority of cases show none, and many patients develop contractures.

The disseminate encephalitides showed different types of multiple central nervous system lesions, such as visual and auditory disturbances, facial palsies, swallowing and speech disturbances, general symptoms such as headache, memory disturbances and general motility and sensation disturbances. Some of these cases seemed to be related definitely to multiple bulbar lesions, and in them dysphagia and dysarthria were particularly frequent. The speech disturbance was long lasting and was still present many months after other symptoms had disappeared. Four cases showed definite spinal cord involvements. They were of the myelitis type, with sensory and motor levels about the lower dorsal segments. Acute hydrocephalus was diagnosed in one case on the basis of periodic headache, vomiting and choked disk. The symptoms came on suddenly two days after cessation of the fever, lasted about three

weeks and then gradually subsided. The four cases of acute ataxia were of the Leyden-Westphal type.

The author does not give the total number of typhus cases from which these were selected, so that the proportional representation cannot be determined. No presentation of pathologic material is made, but the author reviews the literature on the pathologic condition of the central nervous system in typhus. He prefers the view that there are characteristic lesions, as described by Fraenkel and Dawidowsky, in the form of special glial proliferations and vascular lesions. Some of the vascular disturbances may be due to lesions of the cervical sympathetic ganglia. In summarizing, Feldmann concludes that: central nervous system disturbances of a lasting and, at times, even a permanent type may be found in the course of typhus; they show predilection for the motor rather than the sensory system; they affect the facial nerve more frequently than any other cranial nerve, and may cause definite myelitic processes. The occurrence and degree of the central nervous system lesions do not depend on the intensity of the general condition.

MALAMUD, Foxborough, Mass.

PREPAROXYSMAL VESSEL CHANGES FOLLOWING EXPERIMENTALLY PRODUCED HYPERVENTILATION IN THE DOG. W. JACOBI, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:625 (June) 1926.

The observation of Foerster that attacks of epilepsy are stopped by hyperventilation has provoked interest in the status of the vessels during and after an attack. Foerster, in the criticism of his experiments, calls attention to the oldest of the theories relating to the pathogenesis of the epileptic attacks—the vascular theory. Much work has been done on the acid-base equilibrium in epilepsy. Elias has reported a preparoxysmal acidosis and has attributed a greater excitability to nerve tissue as a result of disturbance of the acid-base equilibrium. By experiments on animals, he was able to show changes in the excitability of the brain tissue with disturbance of the equilibrium of inorganic acids; sulphuric and hydrochloric acids caused the least excitability and phosphoric acid was most efficient in causing hyperexcitability of brain tissue. The point of attack is on the nerve trunk or nerve ending. The cerebral cortex is fatigued by acidosis and responds to a lesser stimulus than normally. Elias holds, however, that nothing has been gained in these facts for the pathogenesis of tetany and epilepsy unless an acidosis can be shown to exist at the same time. Rohde considers the slight increase in acid in the preparoxysmal stage too small to act as a cause of the epileptic attack. Frisch, however, has warned that oscillations in metabolism are so striking in epilepsy that no theory of the disease can be constructed which does not take cognizance of these facts. Acidosis and changes in the electrolytic equilibrium become expressions, then, of metabolic disturbances affecting excitability. In addition to acidosis in preparoxysmal conditions, there is retention of chlorides and diminution in calcium. Preparoxysmal acidosis appears to be a big step forward in the understanding of the paroxysmal attack. On the other hand, Jarloev, Bisgaard and Noervig demonstrated a deviation of the blood to the alkaline side in the preparoxysmal stage. Vollmer, too, found evidence of alkalosis in this stage. Auschmann has found carbon dioxide saturation in epilepsy. According to Vollmer, the occurrence of alkalosis in epilepsy differentiates it from tetany.

Since the work of Fritsch and Hitzig on the electrical excitability of the brain, it has not been possible to produce an epileptic convulsion in an animal

by increasing the strength of the electric current. By the production of acidosis, however, through flooding with carbon dioxide it has been possible to produce convulsions similar to epilepsy and to watch the state of the cerebral vessels in such attacks. Herniation of the brain occurred, with venous hyperemia, distinct visibility of the peri-adventitial spaces, and subarachnoid collection of plasma colloids, the latter taking place after the attack. In the preparoxysmal stage, there is retraction of the brain substance and distinct paling through vasoconstriction. As a result of the acidosis the electrical excitability of the brain is increased. Jacobi does not think that the preparoxysmal vasoconstriction is directly related to the epileptic attack, but that instead it indicates a disturbance in the acid-base equilibrium.

ALPERS, Philadelphia.

THE DEVELOPMENT AND EVOLUTION OF MIND: BIOLOGICAL VERSUS PSYCHOSOCIAL INTERPRETATIONS OF THE ONTOPHYLOGENETIC PARALLELISM. IAN D. SUTTIE, J. Neurol. & Psychopath. **5**:133 (Aug.) 1924.

The author quotes Freud, Leonardo da Vinci, Jung, Jones, Lind, Evarts and Van Teslaar in showing that psychanalysts have resigned to biology the interpretation of the resemblance between mental development and mental evolution. He states that they, in doing so, are not clear either as to the data that necessitate the "recapitulation hypothesis" or as to the meaning and consequences of this.

There are two definite questions to consider: (1) the evidence for the recapitulation theory of mind, and (2) the inferences one is enabled to draw. Taking the evidence for mental recapitulation at its strongest, as showing the outcrop of highly specific identifiable fragments of genuine ancestral myths in the patient's fantasy life, a simpler, less onerous interpretation of the facts is to believe these "race memories" are transmitted via "social inheritance" (tradition) rather than through the mechanism of the germ plasm. The factors of experience, education, nursery rhymes, fairy stories, etc., might easily give to the fantasies of childhood the specific archaic forms that lead one to observe a similarity between mental evolution and mental development. Freud's statement that symbolism is "never individually acquired" is laid open to question by a certain nursery rhyme. This sort of thing is taught to the child from his earliest lullabys. It is verbally, not germinally, transmitted. The whole form of the argument for recapitulation rests on the denial of the possibility of a traditional or verbal transmission.

There are many circumstances that tend to mold the person along the general lines of the ancestral history, and their effect is a pseudorecapitulation. In intellectual development, a rough ontophylogenetic parallelism suggests recapitulation. Simple and fundamental ideas must be mastered before more complex and abstruse ones which imply them. Certain discoveries and propositions must precede others. This is logical, not biologic, recapitulation.

When one speaks of the evolution of the human mind, he really means the history of culture, which is not an evolution but a continuous development that is not broken at each generation as is organic evolution. The history of culture and the assimilation of culture are social processes to be explained by social psychology.

The theory adds nothing to the present knowledge nor does it offer any compensation for the violence it requires neurologists to do to the facts.

FAVILL, Chicago.

CLINICAL AND HISTOPATHOLOGIC INVESTIGATION OF CHRONIC VASCULAR SYPHILIS IN THE CENTRAL NERVOUS SYSTEM. MALAMUD, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:778 (June) 1926.

Ranke, Sagel, Ilfeld, Westphal and Sioli have described cases of syphilitic endarteritis, and years ago Jakob studied several such cases clinically and pathologically. Four cases are described in which syphilitic vascular disease was the outstanding picture in the pathologic condition of the brain. Case 1 presented a disease course of eight years, and began with acute confusion and excitement, which were followed by epileptic attacks. With these occurred a slowly progressing loss of mental power, which eventually reached a high grade. Remissions occurred, and at times the blood Wassermann reaction was positive. Pathologically, severe vascular disease was predominant. This was of two kinds: hyaline degeneration in the large pial and basilar vessels, an arteriosclerotic process, and an endarteritis syphilitica of the small pial and cortical vessels. The parenchymatous changes consisted of ganglion cell degeneration and glia proliferation. The process was therefore fundamentally a syphilitic endarteritis of the small pial and cortical vessels. Case 2 occurred in a patient, aged 57, who contracted syphilis at 30, and who first showed a syphilitic meningitis. Then he showed signs of syphilitic meningitis of the cord or tabes, followed by cerebral manifestations. Eight years after the beginning of his illness he had an apoplectic insult with extrapyramidal and cortical lesions, parkinsonism with tremor in both upper extremities, paralysis of the right extremities without a Babinski sign, severe speech disturbance, confusion and excitement. The blood and spinal fluid gave strongly positive Wassermann reactions over a period of eight years. The course was progressive with remissions. Pathologically, there was severe vascular disease of the cerebral arteries with a lymphocytic meningitis which was probably syphilitic. The vascular changes in the basilar vessels were of two kinds: exceptionally, the usual intimal proliferation with fatty deposit and calcification and, usually, marked thickening of the media with hyaline degeneration without fatty deposit. In addition there was lymphocytic infiltration in the adventitia. The cortical vessels showed syphilitic endarteritis. The brain substance showed diffuse chronic parenchymatous degeneration. Case 3 was one of progressive paralysis, a persistent right hemiparesis twenty-five years after an apoplectic insult. Necropsy showed chronic vascular disease of a syphilitic nature.

ALPERS, Philadelphia.

CLINICAL EXAMINATION OF THE SYMPATHETIC SYSTEM. A REPORT BEFORE THE SEVENTH RÉUNION NEUROLOGIQUE, PARIS, JUNE, 1926. G. SÖDERBERGH, Rev. neurol. **1**:721, 1926.

"The subject abounds in diffuse and contradictory opinions so much that a lifetime would hardly serve to place them in order. The present state of science on this subject, the immense literature and the poverty of serious control investigations, schematic theories, and premature hypotheses, present a veritable image of contemporary life with its hasty procedures, its lack of poise and rarity of independent and courageous thought. These last twenty years, period of flamboyant manifestations of advertising and vulgarity, have been equally the golden age of publications on the sympathetic system. The unknown land, as Pierre Marie called this domain, has also been the promised land of many of these authors."

After such an opening the author proceeds to a critical, almost caustic criticism of methods of examination of the sympathetic nervous system, showing how the results of physiologists have been carried over into clinical medicine with little appreciation of their true nature; how classification has been erected and then discarded, and how tests for supposedly one system have been found to act on two. The report is destructive. It deals principally with the pharmacologic tests. Epinephrine, atropine and pilocarpine are discussed. In regard to epinephrine the author states: "Briefly, at present we possess only a mess of curves, some fragmentary, others more or less complete, obtained with different dosage or with groups of individuals passably homogeneous." He sees no real clinical value in any of the pharmacologic tests, except in the case of atropine, to distinguish certain cardiac affections, and of epinephrine in hypertension.

In regard to the oculocardiac reflex, one is again met by a host of dissimilar methods of application. Applied under standard conditions, the test seems to be of value in distinguishing true asthma. Other effects of ocular pressure are still of questionable clinical value. The same might be said of the celiac reflex, cervical vagal pressure, and the obscure intravisceral and intervisceral reflexes. All that can be said at the present time is that the tests allow of neither general classification nor certain guides in the diagnosis or prognosis of disease. Their value is yet to be determined.

FREEMAN, Washington, D. C.

MUSCULAR DYSTROPHIES, SYMPATHETIC SYSTEM AND ENDOCRINE GLANDS. E. BRAMWELL, Lancet **11**:1103 (Nov. 28) 1925.

The author describes at some length the history, the inferences from comparative anatomy and the conclusions from embryologic observations concerning dual innervation of skeletal muscle and describes the relation between these dystrophies and the glands of internal secretion, quoting cases to illustrate his points. In his conclusions, he states that the generally accepted view regarding muscular dystrophies as a primary disease of muscle is a negative conception. He advances the suggestion that perhaps the diseases of the muscle supplied by the sympathetic nerve may be the cause of the dystrophies. Since the muscles that develop early in the fetus and those that are regressive as opposed to those that have acquired a function at a later date and those muscles associated with the function of fixation are the ones most commonly affected in this disease, a difference in the innervation might be considered as a possible causal factor. The histologic picture in muscular dystrophies may be accounted for by postulating a common cause, affecting either interstitial or musclar tissue. Since the symptoms observed in muscular dystrophies cannot be explained by a primary disease confined to the muscle, the author suggests that the atrophic paralysis is merely the most prominent manifestation of a more widely spread process. He suggests further that the gradual loss of power and wasting of the muscle may be either a direct consequence of interference with the sympathetic innervation or a consequence of secondary involvement of the somatic nerve fibrils by the changes in the muscles and interstitial tissue, which result from disease of the sympathetic nerve supply. While familial cases may be due to an abiotrophy of the sympathetic neurons, these isolated cases may have been determined by a toxic neuritis which has selected the sympathetic fibers and produced an atrophic paralysis of similar distribution. Bramwell believes that when pseudohypertrophy occurs, it is an individual rather than a familial characteristic, and that it may possibly be a superadded condition due to a

relative pituitary insufficiency. The author believes also that disturbances of the pineal and other glands of internal secretion occur, but admits that the disturbance of the gland and the muscular dystrophy may be due to a common cause.

At the end of the article is an extensive bibliography.

POTTER, Akron, Ohio.

LEUKEMIA AND THE CENTRAL NERVOUS SYSTEM. B. M. FRIED, Arch. Path. **2**:23 (July) 1926.

With the exception of pernicious anemia, studies of the central nervous system in hemopoietic disorders have been neglected greatly. Reports of only thirty cases could be collected in which the central nervous system had been studied in cases of leukemia. The basis of the study was a case of lymphatic leukemia which, on section of the brain at autopsy, showed many lymphomas. "Two areas of softening were seen in the anterior portion of the frontal lobe, one area on the under surface of the right parietal lobe and two in the occipital region. On cut surface numerous lymphomas, varying in size from 1 mm. to 2 cm., were found scattered throughout the hemispheres." On microscopic examination most of the lymphoid cells were found in the larger blood vessels and in the capillaries which they practically occluded. In the subcortical regions were numerous lymphomas sharply demarcated from the brain substance, made up chiefly of lymphoid elements without admixture of blood. A small lymphoma was found in the cerebellum. Near the large lymphomas the ganglion cells were shrunken or sclerosed, while at some distance from them there was evidence of tigrolysis. The axons were intact, except in the region of the hemorrhages. No gliosis had occurred.

Review of the cases in the literature showed thirteen with bleeding into the brain in leukemia, and this condition seems, therefore, "less uncommon than generally supposed." In three cases the bleeding led to hemiplegia. The low incidence of cerebral lesions in leukemia is explained by the fact that minute hemorrhages often do not give signs, while large hemorrhages occur shortly before death. Reports of seven cases of involvement of the cranial nerves were compiled. In two cases the acoustic nerve was involved, and in five one or both facial nerves. The cause of cranial nerve lesions seemed to be mechanical in origin "due to compression of the nerves by infiltrated lymphoid cells." Eleven cases of involvement of the spinal cord in leukemia also were compiled. In three of the cases, this was due to pressure by a lymphoma that had originated by infiltration in the meninges, and in the other eight instances the process was degenerative.

ALPERS, Philadelphia.

"PNEUMORACHIE." M. M. RISER, Ann. de méd. **20**:52 (July) 1926.

This term is used for the injection of small amounts of air into the subarachnoid spaces in order to ascertain whether the passage is free or blocked by tumors or adhesions. The author rejects ventriculography as dangerous, and claims that his method of injection of 5 cc. of air is harmless. The technic is simple: The patient sits on the bed with the head bent slightly forward; a lumbar puncture is done and 4 cc. of fluid removed; 3 cc. of air, filtered through sterile cotton, is then drawn into a 5 cc. syringe and injected under pressure through the puncture needle. The ascending air bubbles produce a slight sensation of pressure along the spine, which is not painful. At the moment the air passes through the foramen magnum, a pricklike sensation is felt in the back

of the neck. Finally, the patient experiences headache and nausea after the air has passed through the foramina of Luschka into the ventricular system. The last syndrome may continue for twelve hours, with occasional vomiting. If these reactions occur, one may be assured that the passage of the subarachnoid spaces is free and the puncture needle may be removed.

If the patient does not immediately experience the sensations described, two possibilities may be assumed: (*a*) a complete block by compression of a tumor or by pachymeningitis; (*b*) an incomplete block by only partial obstruction of the passage. If the tumor is posterior and adherent to the posterior roots, a sudden injection of from 2 to 3 cc. of air will produce the sensation of an intense, transient pain within the segments supplied by these roots. These phenomena may be used to localize the tumor. In the case of a complete block as the result of pachymeningitis, the cerebral symptoms described will not be experienced by the patient, and the air may flow back through the needle. If the block of the subarachnoid spaces is incomplete, the air will penetrate only gradually, and the subjective sensations of pain in the neck and headache will be felt only after two hours have passed. In the case of complete block a cirternal injection of iodized oil 40 per cent wth subsequent roentgen-ray examination will give an exact localization of the lesion.

WEIL, New York.

PRIMARY TUMORS OF THE OPTIC NERVE AND OF THE CHIASMA, WITH A REPORT OF A CASE. W. G. WYLLIE, J. Neurol. & Psychopath. **5**:209 (Nov.) 1924.

Tumors which chiefly affect the intracranial portion of the optic nerve and the chiasm constitute a difficult problem for the neurologist. Only tumors of subdural origin are considered. They are usually of low malignancy. Contrary to common impression, numerous instances of intracranial as well as of intra-orbital invasion are on record. Most of the tumors are gliomas. Almost the only other type found is the endothelioma. Gliomas usually occur in young people, usually spread centrally from the intra-orbital portion of the nerve and do not infiltrate the dura. Endotheliomas are more common after the age of 30; often they are found in close apposition to the back of the eye and never involve the chiasm. Growth of a type similar to the tumor of the optic nerve may be present in other parts of the brain or its meninges.

Following a discussion of the histology of these two tumors, a case is described in which a glioma affected the intracranial portions of both optic nerves and the chiasm and in which an entirely separate tumor of the same nature was present in the brain.

In symptomatology, emphasis is laid on exophthalmos and impaired vision. In a glioma, the visual disturbance is likely to occur first; in endothelioma, the exophthalmos is earlier. Strabismus is not common but is more likely to be present with an endothelioma. There is usually no complaint of pain. Slight swelling of the disks or atrophy alone may be present. Chiasmal invasion produces symptoms almost identical with those caused by tumors of the hypophysis. The loss of vision in both eyes due to tumor of the chiasm tends to be more rapidly progressive. One would not hesitate to condemn the removal of a chiasmal growth so long as any sight remained. When blindness is complete, other contiguous structures probably will have been involved.

The author discusses the relationship between neurofibromatosis and glioma nervi optici and states that, while it is hard to prove, he believes that there is some justification in assuming that it does exist.

FAVILL, Chicago.

# Society Transactions

## PHILADELPHIA NEUROLOGICAL SOCIETY

*Regular Meeting, Oct. 22, 1926*

W. G. Spiller, M.D., *President, in the Chair*

### Mental Sequelae of Carbon Monoxide Poisoning, with Reports of Autopsy in Two Cases. Drs. E. A. Strecker, A. E. Taft and G. F. Willey.

About a year ago, in a paper presented before this society, Dr. M. C. Borman discussed the pathologic changes in the central nervous system caused by carbon monoxide poisoning, referring to the work of Forbes, Stewart, Alpers, Ruge, Claude and Lhermitte, Fejir, Pineas, Wilson and Winkelman and others. The early work of Hill and Semerak, who examined thirty-two brains, and of Wohlwill, who described eight others, was at that time not mentioned, but the conditions they reported were similar to those reported above, consisting of characteristic symmetrical softening of the globus pallidus, with degenerative changes in the arterial walls leading to the deposit of lime salts even by the third day. Photakis did considerable confirmatory, experimental work with animals, and Muller also described similar observations in several cases, noting the marked increase in the incidence of this form of poisoning during late years.

Since the presentation last year, the same characteristics have been reported in cases of carbon monoxide poisoning by Roy R. Grinker, and to these we wish to add the reports of two cases studied by us in the wards and laboratory of the department for mental and nervous diseases of the Pennsylvania Hospital.

#### REPORT OF CASES

Case 1.—B. Q., an unmarried woman, aged 30, a secretary, was found unconscious in the kitchen of her home in the early morning. She had excluded all ventilation, turned on six burners of the gas stove and had remained there for at least one and one-half hours. She was taken immediately to the hospital, where oxygen and carbon dioxide were administered. The pupils reacted to light, showing hippus, and the eyeballs were in a constant state of nystagmoid movement. Pulmonary edema was present, with Cheyne-Stokes breathing. The temperature showed some elevation, the heart was rapid, weak and irregular and the extremities showed some spasticity, increased reflexes with clonus and double Babinski sign. The laboratory reported the urine to contain a trace of albumin during the first three days, hyaline and light granular casts once, red and white blood cells once, and acetone during the first five days. Thereafter it was normal, except that the specific gravity ranged from 1.030 to 1.035. The leukocyte count was 30,200 the first day, decreasing steadily to 11,000. Tests for carbon monoxide hemoglobin were negative. The stool and the contents of the stomach showed the presence of barbital. The spinal fluid was clear, with one cell per cubic millimeter and no increase in protein or globulin. Venesection, the intravenous injection of salt solution, and transfusion were done the first three days, and the patient was fed by tube. Three convulsions were recorded during the first week, but details were not given.

Unconsciousness continued for twenty-two days, when she began to seem brighter, was apparently able to see, hear and understand, and could take fluids by mouth instead of the feeding tube. Fundus examination on the fourteenth day showed congestion only. The pupils did not react to light, and coarse lateral movements of the eyeballs continued. At the end of the third week spasticity of the extremities was marked with beginning contractures.

A neurologic consultant saw the patient at this time and noted smoothing and restricted movement of the left side of the face, exaggerated, equal reflexes, and contractures of the elbows, knees and distal parts of the extremities. Paralysis was incomplete, and the patient withdrew her limbs from painful stimuli. She became restless, untidy and finally noisy in an inarticulate way, and on the thirty-eighth day was transferred to a psychiatric hospital. There she was noted as stuporous, uttering an occasional whining cry accompanied by flushing and wrinkling of the face, resisting extension of the limbs and withdrawing the limbs from painful stimuli. On one occasion she spoke a few intelligible words in answer to questions, and once said she was tired. Paralysis of the extremities was incomplete, with flexion contracture greater on the right and most marked at the shoulders, elbows, hips and knees. Paralysis of the trunk and the facial musculature was only partial, the left side of the face being most affected. All the muscles were greatly wasted, and all the tendon reflexes were greatly exaggerated; clonus was obtained at the ankles and knees on only one occasion. The abdominal reflexes were continuously absent, but a definite Babinski sign was elicited only once. Fundus examination showed high myopia, without definite retinal or vascular change. The pupils did not react, and even bright light produced no visual response. Flushing of the skin and profuse sweating were present over the entire trunk, and the maceration of the skin had produced bedsores of the back and buttocks before the end of the fourth week. Trophic disturbances were shown, and the patient was incontinent of urine and feces. Liquid and soft nourishment and water were swallowed well, but solid and semisolid nourishment was never taken. The pulse was more than 120 a minute most of the time, and the respiration mainly above 30. The urine continued normal, except for a trace of albumin at one examination. The blood showed a moderate secondary anemia, with 13,000 leukocytes. The spinal fluid was clear, contained 15 cells per cubic millimeter, an increase in albumin, globulin and sugar, and a mastic curve of 0001113331. The spinal fluid Wassermann reaction was negative; blood for a Wassermann test was not obtained. A roentgenogram of the cranium was normal. A condition resembling mucous colitis developed. The temperature, which had previously run an irregular febrile course as high as 104, rose to 105, 106, 107 and 108, with a pulse rate too rapid to count and respirations of 55 a minute. The peripheral circulation apparently ceased and the extremities became cold and livid, with a rapid, weak and irregular heart beat which ceased at least five minutes before the breathing stopped. The patient died on the fifty-third day after the exposure. Owing to difficulty in obtaining the services of the coroner, postmortem examination was deferred until about eighteen hours after death.

Case 2.—L. E., a professional man of marked attainments, was found in his apartment unconscious from illuminating gas to which he had been exposed when an open gas burner was extinguished in the kitchen. He had probably been breathing this atmosphere for several hours, and was saved from suffocation only by an open window. He was taken at once to a hospital and arrived

with Cheyne-Stokes respiration, a full bounding, regular pulse, marked spasticity of the extremities and a dusky red color. The pupils were dilated and equal, but did not react to light. He remained in the hospital for eleven days, during which the temperature was normal, respirations were around 20 a minute, and the heart rate from 90 to 100, except that during the first day it ranged as high as 150 a minute.

The first specimen of urine obtained by the catheter showed albumin and many casts and crystals. Later specimens showed a trace of albumin. The kidney function test showed 25 per cent elimination in one hour and a total elimination of 45 per cent in two hours. The laboratory reported nothing else of importance except a moderate secondary anemia and a leukocyte count of 14,000.

Fluids were given by hypodermoclysis and enteroclysis at first; the patient had to be urged to take food, because after the earlier confusion and incoherence had cleared up he expressed himself as "tired of everything" and seemed depressed and listless. Progress was uneventful, and on the eleventh day after the accident, he returned home, where he continued inactive, easily fatigued, and mentally indifferent, but without serious symptoms for twelve days, when he died suddenly.

The previous history showed no physical or infectious disease which could be connected in any way with the autopsy observations.

### PATHOLOGIC REPORT

Gross examination revealed no specific changes on the outer surfaces of either brain. In case 2, there was considerable atherosclerosis of the basal vessels. In case 1, frontal sections showed small softened areas in the globus pallidus on both sides. The corpus dentatum on both sides also was degenerated. There was general hippocampal atrophy with a consequent wide space about the crura.

The significant microscopic observations were similar in the two brains, and varied mainly in degree. In case 1, the softened areas, seen grossly, appeared as broken down tissue infiltrated with large, compound granule cells. There were also many miliary softenings found only in this specimen, which was from the case of longer duration. In case 2, changes in the basal gray matter were present, but had not gone on to cystic softening.

The most outstanding alteration was present in the white substance throughout, in which there was diffuse infiltration by various types of glia elements, mainly large, protoplasmic forms, and focally, many endothelioid cells of the compound granule type, which were shown by the scharlach R. stain to be filled with fat. These fat laden cells appeared in perivascular spaces as well as interstitially. The alterations in this type of poisoning are generally considered as due to anoxemia, since carbon monoxide is said to have 200 times greater affinity for hemoglobin than oxygen. Changes in the globus pallidus in carbon monoxide poisoning have been recognized for a long time.

The diffuse reaction in the white substance has been reported seldom. It is apparently the result of a severe alteration in the myelin; a definite myelinopathy, which leads to marked disturbance of function and, when sufficient in degree, is unrecoverable.

Report of a similar case has been made recently by Grinker, in which he characterizes this lesion of the deeper white matter as extraordinary and interesting.

DISCUSSION

DR. N. W. WINKELMAN: I think that Dr. Strecker might have seen the patient reported by Dr. Wilson and myself who lived for a considerable time after the gas poisoning. In the central nervous system there were much more marked and uniform changes than in Dr. Strecker's case. In this case, the cortex particularly was involved.

TWO CASES OF UNILATERAL ATROPHY OF THE HAND. DR. A. M. ORNSTEEN.

The first case was that of a man, aged 50, who, after definite exposure to a strong cold draught of air blowing directly on the right side of the neck, developed pain in the right arm with weakness of the hand within six hours after the exposure. He had severe pain for several nights which disturbed sleep. The weakness of the hand continued; he had to use the left hand to do his work, which was slaughtering cattle. This occurred about two years ago, at which time no neurologic examination was made, but from the fact that he could not recognize objects by touch in the affected hand, I presume that there must have been a defect in sensation. About three months after the onset of this acute condition, he noticed atrophy of the small muscles of the hand. The weakness of the hand has improved during the past year; he is able to recognize objects by touch, can write and can hold a match firmly enough to strike it, which he was unable to do before; this shows definite improvement. The affected muscles in the hand and forearm show evidences of electrical reaction of degeneration. There is no Horner's syndrome in the right eye, neither is there an increase of reflexes of the lower limbs. The left hand is normal. The case appears to be one of a peripheral neuritis following exposure to cold with atrophy of the small muscles of the hand.

The second case was that of a woman who has atrophy and weakness of the left hand. In February, 1926, while holding a newspaper, she experienced a sharp contraction of the middle finger of the left hand, which remained so for a few moments in sharp flexion. This repeated itself on several occasions in the ensuing three or four weeks. The hand became progressively weaker until now it is almost completely paralyzed. In the past few weeks, the weakness has extended up the arm to the shoulder. There is muscular wasting in the hand, and there is an edema such as is seen in syringomyelia. There are no sensory changes. The electrical reactions in these muscles are of partial degeneration. The reflexes of the lower extremities are markedly exaggerated. There is a Horner's sympathetic palsy on the left. The condition is considered to be a beginning amyotrophic lateral sclerosis. Serologic studies have been negative for syphilis, and spinal manometric studies negative for obstruction.

These cases are presented together because of several interesting points. In the man, in whom, as the more likely cause of the atrophy, one would expect to find a spinal condition, there is a peripheral lesion; in the younger person, the woman, there is a spinal disease. The older patient presents atrophy in a distribution that is usual in spinal disease following exposure to cold and peripheral neuritis. The patient had almost forgotten the acute attack of pain several months before the atrophy was noticed, so that on the surface it appeared that the atrophy was the beginning of a spinal disease such as the woman has. This is somewhat comparable to atrophies of the small muscles of one hand without explicable cause, apparently, in persons who have had an injury of the elbow many years before, which, as the result of the overgrowth of callus,

has irritated the fibers of the ulnar nerve and produced atrophy years afterward. The latter condition is, of course, a neuritic atrophy.

In the case of the woman, the interesting point is that the initial symptom was a myotonic state in the flexor muscles of the forearm.

DISCUSSION

DR. F. X. DERCUM: It seems impossible to determine definitely the etiology of the case. A number of years ago, I reported two cases of men suffering from sunstroke who developed multiple neuritis. One does not know what happens in sunstroke but, at any rate, there was a multiple neuritis without a toxic or infectious cause. It seems to me impossible to settle definitely that question because one cannot get a good history of the time of onset. I remember one case in which a man was exposed to severe cold, and who suffered from a typical multiple neuritis; there was no infection.

DR. A. M. ORNSTEEN: The question of exposure to cold and neuritis is always interesting and is often questioned, but when one recalls the number of Bell's palsies that occur, in most instances after exposure of that side of the face to cold, one would not hesitate to accept the statement that exposure to cold can produce a peripheral neuritis. The question of focal infection operating with exposure to cold in the production of neuritis is to be considered also. Again referring to the cases of Bell's palsy, it seems that the exposure in most cases is the sole etiologic factor operating, since many patients give a history of having had facial palsy years before with apparently good health since, indicating the absence of serious infectious agents or, at least, their benign nature, so that they probably have had no part in the production of the facial palsy, I have noticed that when there is much oral infection in a case of Bell's palsy, the paralysis is usually more severe and the recovery is not complete whereas, in younger persons with good oral hygiene, the prognosis of facial palsy is usually much better, so that I believe when exposure to cold is the sole factor the prognosis for the paralysis is good. When infection is added to the picture, the prognosis becomes more serious.

TWO CASES OF DEVELOPMENTAL DEFECT IN SISTERS WITH MYASTHENIC CHANGES. DR. H. H. HART.

The cases presented occurred in two sisters, from the service of Dr. T. H. Weisenburg in the Orthopaedic Hospital and Infirmary for Nervous Diseases. Their ages were 17 and 19, respectively; they were born in Poland of Jewish parents. The only significant fact in the family history was the death of the father from diabetes at the age of 61.

CASE 1.—*History.*—The younger sister, Anna, came to the hospital complaining of a general tired feeling, general weakness in the muscles and weakness in opening the eyes. The only previous illness had been measles. The menses started at 11½ years and occurred regularly every four weeks until 1923, when they recurred every three weeks and lasted six days. She had noticed that she felt weak for two weeks before each period, and was much better for about five days afterward. The present illness began about 1918, at the age of 9. The patient noticed gradually increasing general weakness. This was noticed especially during the first two years, and in the last year had been so pronounced that she could scarcely walk a block without excessive fatigue. At the same time she complained of drooping and weakness of the eyelids; when she endeavored to read or write she suffered from pain in the eyes.

This weakness increased in the afternoons. In June, 1924, she was admitted to the Mount Sinai Hospital, New York, where the diagnosis of myasthenia gravis with encephalitis was made.

*Examination.*—The patient was of short stature, with a tendency to obesity and pallor. The pendulous breasts and abdomen, quite unusual in a girl of this age, were particularly striking. The musculature was weak and flabby but showed no atrophy. The patient seemed to be older than her stated age. The thorax was long and shallow; the breathing was shallow, but there were no râles or signs of tuberculosis. The heart showed slight enlargement with a systolic murmur over the mitral area. Cardiovascular function, as measured by the Trentsch rating scale, was 0, showing deficient power of the heart muscle. Two badly abscessed teeth were found and subsequently extracted.

The cranial nerves were normal except for bilateral ptosis, which was marked, and weakness of the extrinsic muscles of the eyeballs, which prevented complete lateral and upward deviation of the eyes. This action was readily fatigued. No paralysis was noted in the limbs, but the strength was uniformly and generally diminished and there was marked exhaustibility. There was no incoordination, loss of tonus, or involuntary movement of any kind.

Laboratory examination revealed a trace of albumin in the urine but no glycosuria. The erythrocytes numbered 4,610,000; the leukocytes numbered 10,600, and the differential count was normal. The fasting blood sugar varied from 87 to 111 mg. per hundred cubic centimeters. The nonprotein nitrogen and urea were within normal limits. The basal metabolism was plus 6. Blood and cerebrospinal fluid Wassermann reactions were negative. A roentgenogram of the mediastinum showed no evidence of a persistent thymus. The sella turcica was normal. The vertebral column showed a right dorsal, left lumbar scoliosis with slight rotation of the bodies. Sugar tolerance was subnormal, the blood sugar rising to 289 mg. per hundred cubic centimeters, and remaining as high as 240 mg. at the end of the third hour, while at the same time the urine showed 0.9 per cent sugar.

At weekly intervals the muscles were tested with faradic and galvanic currents without revealing any reaction of degeneration, though the muscles of the lower extremities on one occasion were found to react less promptly to faradism than to galvanism. Pharmacodynamic tests showed considerable reaction to epinephrine but little to pilocarpine.

Case 2.—*History.*—The older sister presented features similar to the foregoing but of diminished severity. The past history showed no more serious condition than measles at 1 year of age, tonsillectomy in 1924, and adenoidectomy in 1925. Menses began at 14 years; they were regular, lasting from four to five days, and the patient noticed no variation in the condition except a slightly increased weakness during the first two days of menstruation.

The present illness began at about the age of 14, at the onset of menstruation, just as in the case of the younger sister. She complained at this time of a sensation of heaviness and general exhaustibility which was increased by a moderate amount of exertion. This condition was specially noted during the first two years. She felt stronger in the mornings, exhaustibility being more marked in the afternoons. At the age of 14, weakness and drooping of both eyelids was noticed, and in 1925 she underwent an operation to relieve the ptosis, which enabled her to see better. Since June 30, 1926, she has complained of occasional diplopia and at night the eyes feel extremely tired. Reading for an hour is quite sufficient to produce this reaction. She has had

no weakness in mastication or deglutition; there have been no sensory symptoms and no decline in weight.

*Physical Examination.*—The patient was less obese than her sister and showed less tendency to pendulous breasts and abdomen. The lungs and heart were normal. Examination of the ears showed a residual otitis media.

Examination of the cranial nerves showed the same restriction of ocular movements in all directions. No paralysis or strabismus was observed, yet she showed diplopia in all directions. The facial musculature showed some weakness with flattening of the nasolabial folds. General muscular exhaustibility was the chief complaint. She had a firm grip in both hands but became quickly exhausted when the movement was repeated a number of times. All the reflexes were hyperactive; the plantar response on both sides was flexion. The pupils were normal.

*Laboratory Examination.*—There was slight albuminuria without casts. The erythrocytes numbered 4,670,000; the leukocytes 5,200, and the hemoglobin was 83 per cent. The average fasting blood sugar was 102.5 mg. per hundred cubic centimeters; the nonprotein nitrogen and urea were normal. The basal metabolic rate was plus 6. The Wassermann reaction with the blood was negative. The sugar tolerance as contrasted with the sister was normal. Roentgenograms showed no evidence of a persistent thymus. The sella turcica was small but normal. Over three consecutive weeks the muscular reactions were tested, but no myasthenic reaction was found. When placed on a creatine-free diet for three days, she showed only 2.88 mg. per hundred cubic centimeters in the blood, and a faint trace of creatine was found in the urine.

### COMMENT

These cases are of interest because of several outstanding features: (1) the occurrence of a myasthenic condition in two sisters; (2) the prominence and early development of ophthalmoplegia and ptosis, first reported by Goldflam and, according to Oppenheim, by no means uncommon; (3) the onset of symptoms at puberty with the beginning of menstruation; (4) the absence of myasthenic reactions; (5) the presence in the younger sister, with the more advanced myasthenia, of a definite developmental anomaly probably associated with endocrine defect and combined with a decreased sugar tolerance. The occurrence of developmental anomalies is by no means rare in myasthenia. Kurschmann and Hedinger have reported myasthenia with sexual infantilism and hypoplasia of the genitals. A persistent thymus is probably in itself a congenital developmental anomaly. Cases have been ascribed to parathyroid and suprarenal deficiency, others to liver autointoxication, but no satisfactory theory has yet emerged from these endocrinologic observations.

## A Case for Diagnosis. Dr. M. A. Burns.

A theological student, aged 20, whose chief complaints were generalized weakness, difficulty in walking and nervousness, presented an unimportant family and past history. His general health had always been good. He had had measles and whooping cough, an attack of tonsillitis at the age of 17, and pneumonia at 9; there had been no other acute infection. Two years previously he had been sent abroad to an Italian theological seminary, where the discipline was rigid, and he was obliged to speak the language as well as

he could from the beginning. The discipline was so severe that all students were locked in their rooms at night and had little or no exercise. After fourteen months of this life, the patient suffered a collapse. He was treated in the infirmary of the seminary for a time and was then sent to a hospital in Rome where a diagnosis of functional neurosis was made. He was treated by suggestion and electrotherapy and in a slight measure the condition cleared up. He returned to the seminary after six weeks in the hospital, and was only back three or four weeks when he had complete paralysis of all four extremities following a hike. He was again taken to a hospital where a diagnosis of multiple sclerosis was made.

He was admitted to Jefferson Hospital, in Philadelphia, on Sept. 8, 1926. He had difficulty in walking and a peculiar fixed attitude. The station was more or less guarded; he had a peculiar gait which superficially appeared spastic, but on further examination did not present any spasticity of the lower limbs. When he walked he did not swing the arms. When he turned, he turned the entire body like one suffering from parkinsonism. The reflexes were markedly increased, but there was no evidence of a Babinski sign or of ankle clonus and no definite spasticity in the upper or lower limbs. The abdominal reflexes were absent. There was no sphincter disturbance and no sensory loss anywhere. The eyegrounds were normal, but there was a suggestion of lateral nystagmus at times; it was thought to be present at one examination and later, when examined again, was not found. The blood and spinal fluid Wassermann reactions were negative, and there were four cells to one cubic centimeter of spinal fluid. Three possible diagnoses were suggested: (1) insular sclerosis; (2) epidemic encephalitis; (3) hysteria.

#### DISCUSSION

Dr. F. X. Dercum: This case strongly suggests the parkinsonian syndrome group, the sequelae of encephalitis or perhaps an irregular or atypical form of paralysis agitans.

Dr. Alfred Gordon: Not knowing the previous history and judging from the symptoms presented and as it stands today, I think that this case is one of parkinsonism. The gait, attitude, facies, etc., all point to this diagnosis.

Dr. E. A. Strecker: The two or three distinct exacerbations, taken together with the picture he presents now, with absence of abdominal reflexes, make me feel that it is a case of disseminated sclerosis. There was not much in the history to suggest encephalitis, no diplopia and no eye muscle signs.

### Minute Vascular Cortical Lesions. Their Formation, Appearance and Clinical Significance. Dr. N. W. Winkelman.

The author showed lantern slides of cortical sections with minute areas of softening, dependent on vessel occlusion. Every stage was represented, from the earliest coagulation to final scar formation. In regard to clinical interpretation, stress should be laid on the fact that in most of the well recorded histories cerebral attacks of some sort were described which lasted from hours to days. The symptoms naturally depended on the site of the lesion. In some, periodic attacks of confusion occurred; in others temporary aphasias or paralyses. While a few such areas may occur without permanent sequelae, many such foci of softening would lead to permanent defects.

DISCUSSION

DR. ALFRED GORDON: It has been proved experimentally that quinine produces spasm of the blood vessels in the retina. Cases of that character are on record; there was contraction of the walls of the blood vessels at first, and then they reopened. Dr. Cushing has observed contraction and relaxation of pial blood vessels from epinephrine.

A patient of mine complained of having, several times during the year, sudden and transient weakness of the right arm. Another, in addition to the same weakness, had some disturbance of speech of a similar character; this occurred several times during his life. Both patients were kept under observation, and finally complete hemiplegia occurred. The only thing that I can figure out in such cases is that a spasm occurs and the blood vessels open up again, but repetition will necessarily bring on a final and permanent paralysis.

DR. CHARLES POTTS: Does Dr. Winkelman think that a condition similar to that which he has shown occurs in migraine? It seems to me that migraine is a different thing, clinically and pathologically.

DR. N. W. WINKELMAN: The point I wanted to bring out was that which Dr. Gordon mentioned. Even if the symptoms clear up, it does not mean that there has been no lesion. The lesion is small, and the clinical symptoms last only a short time. The question of migraine brings up a point that I carefully avoided. I do not believe that in any of the cases I showed you there was a history of periodic headaches, and it is hard to conceive of these occurring in migraine, especially in persons who have two or three attacks a month. There would not be enough room in the cortex.

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## CHICAGO NEUROLOGICAL SOCIETY

*Regular Meeting, Oct. 28, 1926*

JOHN FAVILL, M.D., *President, in the Chair*

A CASE OF SCLERODERMA. DR. HUGH T. PATRICK.

This patient is 19 years old, a student-teacher, unusually intelligent and capable. The personal and family history are unimportant, except that one sister died at the age of 2 years of what apparently was poliomyelitis. The tonsils were removed at the age of 13, as a prophylactic measure, there having been no symptoms connected with them. She began menstruating at 14, the periods occurring from every four to eight weeks. In November, 1925, she turned the right ankle. There was not any discoloration or pain, even when walking, but swelling was noticed immediately, and because of this she was put to bed for a week. Still pain was not elicited by walking, but soon afterward the right ankle appeared red and was somewhat tender; it hurt when pressed or pinched. She then went to a chiropractor who said she had flatfeet and gave her arch supports. Soon the left ankle was noticed to be swollen. The swelling gradually extended up the legs. By March, 1926, she noticed what she termed a "hollowing out" of the right ankle in the region of the Achilles tendon and several weeks later she noticed a similar appearance about the left ankle. During April, two or three slightly raised red bars appeared over the right ankle, but were not painful. A physician made a diagnosis of purpura rheu-

matica, but there was not any pain. By May, slight depressions began to appear where the red streaks had been.

The girl came to me on Oct. 2, 1926. For a month preceding that time she thought that the legs had become fatigued more readily than before and that they felt a little stiff. A short time before, a diagnosis of muscular dystrophy had been made. When I looked at the legs with the stockings off, I perpetrated the worst Irish bull of my life. I said that this young lady has facial hemiatrophy of both legs. The fat and subcutaneous tissue have largely disappeared in the "hollowed out" regions and in these atrophic areas the skin is thin, slightly brown or yellowish, rather shiny and parchment-like, such as one sees in facial hemiatrophy. I have seen a case of typical facial hemiatrophy with similar atrophic areas of the legs. This case is one of generalized scleroderma, except that it does not involve the face. It is most marked in the gluteal region and upper arms but has improved somewhat with the administration of thyroid and ovarian substance. In a way I can see how one might think it a case of pseudohypertrophic paralysis, but there is no paralysis of any sort. Neither the sclerosis nor the atrophy involve the muscles.

Scleroderma is not infrequently associated with facial hemiatrophy. The disease is not understood. It occurs with various trophic and vasomotor complications. Although the etiology is unknown, the prognosis is not necessarily bad. Some of the patients recover. While this has been almost an acute case, the patient is certainly better as regards the scleroderma. I am watching the hollowed out places to see if the condition is progressing. The patient thinks they are, but I cannot see any signs of progress. She is taking thyroid and ovarian substance.

A Case Showing a Myasthenic Syndrome Following Encephalitis. Dr. George W. Hall.

A minister, aged 61, was referred to me by Dr. Gilbert; he had been a patient at the Mayo Clinic. In February, 1926, he had encephalitis with diplopia on one or two occasions. He made a good recovery, except that the left eyelid drooped from that time. In June, he noticed a feeling of tightness about the muscles of the throat, and when speaking from the pulpit found that within a few minutes he would have to stop because his voice would give out. In June also he noticed weakness in the jaws. After eating for a few minutes he could not get the teeth together, and after winking the eyes a few times he could not get them open. The report of the examination at the Mayo Clinic, which was obtained from Dr. Parker, gave a diagnosis of myasthenia gravis. The pupils react to light and in accommodation. The drooping of the eyelids is worse in the evening than in the morning. At night the right eyelid shows decided drooping; in the morning he will be able to open the eye in a normal way, but the left eyelid droops all the time. The left arm is weak, but there is no weakness in the lower extremities.

I am presenting the case as one of encephalitic origin. With electrical tests I was unable to get the typical myasthenic reactions. In a brief review of the literature I find that some authorities mention that in postencephalitic cases the patients do not show the myasthenic reactions. They make that a differential point between this type and the true myasthenia gravis.

Question: Was lumbar puncture performed?

Dr. Hall: Yes. The cell count was normal, and there was a slight reaction in the third and fourth tubes with the colloidal gold test, if I remember correctly. The test was made at the Mayo Clinic, and I did not repeat it. Otherwise the fluid was regarded as normal.

DISCUSSION

PROFESSOR WIMMER, Copenhagen: This is a most interesting case. I have seen two similar cases, reports of which I have published in the *Revue neurologique*. The patients were about the same age, one a little younger than the other, and the disease started in about the same way. One was a markedly acute case of encephalitis; in the other there was diplopia but not any other signs. In both patients there was a pronounced bulbar syndrome. One case did not start with the bulbar syndrome but with weakness of the hands. The patient was in a circus and had to carry people on his hands; he was obliged to give this up and become a musical clown, but he had to give this up also because his voice became weak. Wasting of the bulbar muscles also occurred. The interesting thing is that both of these patients have improved considerably. One had such marked bulbar symptoms that I was afraid he would die, but he has recovered to the extent that he can take long walks; his wife thinks he has recovered splendidly. In the first case, the one that started with a real bulbar syndrome, there was a true myasthenic syndrome at first. When the man came into my service and I saw him for the first time, which I think was in 1921, this myasthenic reaction had disappeared; in the other case it could not be elicited. I do not think it is true, judging from my own cases and from the literature, that one cannot get the true myasthenic reaction in cases of this sort. The reaction is not vital to the diagnosis of myasthenia. It has been found in other cases, and it has been stated that in some cases it precedes the degeneration reaction. It is interesting because it seems that one has to deal with a toxic influence. I am not sure that one has to deal with toxic influences in encephalitis, but I cannot see why the localized lesions of the centers, in the beginning when the destruction is just setting in, should not produce a myasthenia gravis reaction of the muscles.

HERPES ZOSTER OF THE QUADRIGEMINAL NERVE. DR. A. L. SKOOG (by invitation).

Because of the three sensory and the motor divisions, I prefer the title quadrigeminal to the more usual trigeminal nerve. Herpes is more common in the region of the first than of the other two divisions, where it is quite infrequent. Of 412 cases investigated by Henry Head, the fifth nerve was involved in twenty-two, in eighteen of which the ophthalmic branch was involved. More than half the cases of herpes zoster ophthalmicus are complicated by disease of the eyes, such as acute keratitis, infection of the anterior chamber and glaucoma. This form of herpes is more frequent in persons over 50 years of age. In view of the infrequency of the condition, the following case report is of interest.

A. D., a man, aged 58, was admitted to my service at the Kansas City General Hospital on Feb. 9, 1924, and died, March 10, 1924. He had had the eruption, with some discomfort in the same area, for two weeks. The eruption, vesicular and pustular in character, was limited to the area of the first division of the right fifth nerve including the side of the nose, the upper eyelid and the forehead, whence it extended for a short distance into the hair. The lower eyelid and the cartilaginous portion of the nose were not involved. Vision was absent in the right eye in which there was acute conjunctivitis with inflammation of the cornea, sclera and anterior chamber; vision also was impaired in the left eye. The right pupil was inactive, and the light response was absent in the left pupil which was small and irregular. Hearing was greatly reduced on both sides. Arteriosclerosis was marked with the systolic blood pressure 122 and the diastolic 66; chronic valvular and myocardial disease with auricular fibrillation was present. The Wassermann reaction was

strongly positive with both the blood and the spinal fluid, and the latter contained 10 lymphocytes and gave a colloidal gold reaction of 0013410000.

At necropsy severe arteriosclerosis, myocarditis, valvular cardiac lesions and chronic nephritis were present. Death was caused by these conditions and not the herpes, the acute phase of which had subsided at the time of death, though the panophthalmitis and keratitis had not shown any improvement.

In my opinion the pathologic condition of this disease is still questionable. If the primary inflammatory lesion is in the ganglion why are not all three branches more commonly affected together? In some cases the lesion may be in the ganglion, in others it may be interstitial in the nerve trunk. Involvement of the root posterior to the ganglion should be questioned. Whether it is a specific infection is not established, but it undoubtedly is an acute infectious disease.

DISCUSSION

Dr. Ralph C. Hamill: Were inflammatory reactions found in the brain stem? I have seen two cases of herpes zoster of the thoracic region in which definite inflammatory reactions were present in the posterior horns of the corresponding segments of the cord, conditions resembling those of poliomyelitis. Evidently there was a posterior myelitis in those cases of herpes in which clinically there was nothing but the herpes itself.

Dr. A. W. Adson: At the Mayo Clinic we have had considerable experience in the treatment of herpes ophthalmicus, and I am impressed with the fact that the disease is similar to intercostal herpes zoster. In two patients, I attempted to relieve the pain associated with herpes ophthalmicus by dividing the sensory root of the ganglion, but I am sorry to report that both patients continued to have pain following successful division of the root. In a patient, aged 70, I performed an avulsion with slight improvement only, the improvement consisting of relief from pain when the patient put on his hat; in other words, putting on his hat did not initiate an attack of pain. I am more or less disappointed in the treatment of this disease, and I feel convinced that it is a disease not only of the ganglion but of the pons as well.

With reference to the groups of cells in the ganglion, I feel sure that the gasserian ganglion does not exist as a mass of ganglion cells but that there are three distinct groups, for I have observed that if a portion of the ganglion is accidentally traumatized when the sensory root is being divided, definite hyperemia of the conjunctiva will develop immediately after the operation. If the outer portion only is exposed during the division of the sensory root, hyperemia or conjunctivitis will not develop. I have observed, also, that herpes is a common phenomenon following operation on the ganglion, and I venture to say that about one fourth of the patients in whom division of the sensory root is performed for trigeminal neuralgia develop herpes postoperatively. As a rule, the herpes persists for from four to eight days and then disappears without leaving scars. It has been my observation that the herpes developing postoperatively is prone to be distributed over that area of the face supplied by the particular division in which the pain existed. We have made numerous bacteriologic studies of the ganglion in cases of trigeminal neuralgia, but up to the present time Dr. Rosenow has not been able to demonstrate the organism. It is possible that an active organism exists at the time of operation, and that the failure to demonstrate it is caused by the inability to culture the organism.

Dr. Hugh T. Patrick: I think that the three sensory branches of the fifth nerve correspond to the sensory roots of three spinal nerves and that the

gasserian ganglion is really a fusion of three sensory ganglia. This would account for some of the clinical features of herpes.

I should like to say with a good deal of emphasis that there is not any such thing as typical herpes zoster. There are many types, from the one in which the patient is only conscious of the skin eruption to the cases in which the pain is so intense and prolonged that it wears out the patient. I had one patient, an old man, who certainly died of herpes zoster. He could not be relieved and wore himself out walking up and down and was glad to die. There are all grades between these limits, and the relation of the eruption to the pain seems to be devoid of rule. Dr. Adson has seen a herpes-like eruption appear after a radical operation. In several instances I have seen it appear after injection of the nerve.

I also wish to speak of two therapeutic procedures that are sometimes successful, though I do not know why. Some physicians say that a sure cure is to paint the eruption with pure carbolic acid and wash it off with alcohol. I do not doubt that this sometimes succeeds perfectly, but on other occasions it does not succeed at all. I have relieved the pain of supra-orbital herpes by injecting the nerve at the notch. If the disease is in the ganglion why should such an injection stop the pain? In other instances I have injected and have not secured any results at all. In one case I injected at the posterior pole of the orbit, the patient having already lost the eye. This did not give relief.

Dr. Frank A. Ely: I was interested in what Dr. Patrick said regarding injections of alcohol. On two occasions I have resorted to the use of such injections for the relief of supra-orbital pain following shingles. In both instances the disease had developed in aged men, and had left them suffering greatly. There were marked trophic changes in the skin of the forehead in both cases. I approached the treatment with some temerity, but was gratified by the results. Both patients experienced immediate and lasting relief from the pain.

Dr. Loyal Davis: I might add a little to the confusion because of the remark of Dr. Adson regarding the congestion of the sclera following operation. I have also noticed that the patient has a narrowed palpebral fissure and other symptoms typical of a Horner's syndrome. That has always been true in cases in which difficulty has been encountered with the cornea. It occurred to my associates and me that we might try to find out something about the matter experimentally. A typical Horner's syndrome can be produced in a cat by removal of the superior sympathetic ganglion. Horner's syndrome then can be made to disappear completely by performing a trigeminal neurectomy on the same animal. The converse of this procedure produces the same results. My associates and I also have studied this matter histologically. Our results are not complete, but we have found that in cats there is a group of cells which follow down close to the ophthalmic division of the ganglion. We have also made fiber counts following sympathectomy. We have a feeling, which we think will be conclusive, that in the cases in which we have a disturbance of the cornea following neurectomy we are definitely injuring the sympathetic supply to that cornea. This is borne out in many clinical cases in which we have the small pupil and narrow palpebral fissure on the side of the neurectomy.

Dr. Peter Bassoe: Within the last few months, Potts of Philadelphia reported a case of herpes of this type in which there was a distinct paratrigeminal-sympathetic syndrome. The pupil was narrow and did not dilate with cocaine. The assumption was that there was a lesion of the sympathetic nerve close to the gasserian ganglion, as has been described in cases of small tumors.

A Norwegian, Raeder, reported the first case of that kind, a small endothelioma which affected one corner of the ganglion and involved the sympathetic filaments around the carotid artery.

DR. PATRICK: I understand that Dr. Bassoe has relieved the pain of intercostal neuralgia by injecting into the intervertebral foramen. How is this done?

DR. BASSOE: I think the explanation is that the dendron constitutes such a large volume of the neuron. One must assume that the whole neuron is a unit, and if he destroys a large portion of it the whole neuron suffers. It also may be assumed that an actual retrograde degeneration occurs, with axonal reaction in the nerve cells of the posterior root ganglion.

DR. SKOOG: Regarding Dr. Hamill's question, I will say that the brain removed in this case is the only one I have ever had an opportunity to see, and it was not well cared for. A general pathologist did the work and did not take good care of the specimen. I looked at some of the specimens of brain tissues and could not determine any inflammatory reaction. That is an interesting question and worthy of serious consideration if one can obtain proper autopsy material.

Dr. Adson's remarks were interesting. It is possible that he is correct, but I do not know as yet. Along that line, with regard to Dr. Patrick's report of herpes after injections of alcohol, I have had one case in the course of the third division. It was not pronounced, and I do not think it occurs often. I would suggest that it is a peripheral affair rather than a disturbance of the ganglion itself.

I was interested in the experimental reports of Dr. Davis. That may have some bearing on this complex problem but, as has been intimated by Dr. Patrick, the real pathology and etiology of this condition has not yet been solved.

OBSTRUCTION OF THE LONGITUDINAL SINUS. REPORT OF TWO CASES. DR. JOHN B. DOYLE (by invitation).

This article will be published in full in a later issue of the ARCHIVES.

THE ULTIMATE RESULT IN SEVERE CRANIOCEREBRAL INJURY. DR. THEODORE T. STONE.

Fifty-four cases of severe craniocerebral injury were studied from six to eighteen months after the original injury, and the following conclusions were reached: Craniocerebral injuries in children are much more common than is ordinarily suspected, as many of the patients not showing marked manifestations are probably not brought into hospitals. In view of the fact that my period of observation does not exceed eighteen months, I am unprepared to say whether such injuries in young children have any deleterious effects on their future development, but intend to make a further study over a prolonged period to determine this point.

Two important predisposing factors in the production of craniocerebral injuries in adults are alcohol and the automobile. Coma, in my experience, was not a major sign of prognostic value. Even persistent coma was not always associated with death or serious complications. Dilatation of the pupils with failure to react to light, as well as persistent absence of deep reflexes, was a serious prognostic manifestation.

In 86 per cent of the cases blood was present in the spinal fluid, but I could not attach any prognostic value to this sign. The escape of spinal fluid from

the nose, ears and mouth was not observed in the entire series. The cranial nerves were involved in ten instances, with recovery in all but one case.

Study of the patients at a more remote date showed that complete recovery occurred in 74 per cent, partial recovery in 18 per cent, and about 8 per cent failed to improve. The average duration of illness following these injuries was forty-five days. Permanent remote sequelae consisting of headache, vertigo, emotional changes and several other phenomena, were not as frequent in my series as in those reported by others. In the vast majority of my patients the earning capacity was not materially reduced.

DISCUSSION

Dr. A. L. Skoog: One interesting case that came under my observation was that of a boy, aged about 14, a rather lively youngster, who fell off a truck to the cement paving. He got up and ran home. The family physician was called and suspected a serious injury to the brain. The boy then came under my observation and I found a fracture of the skull in the occipital region, blood in the spinal fluid, and some mental confusion which cleared up in a day or two. The interesting feature of the case was that an ophthalmologist had been treating a congenital strabismus which had improved about 80 per cent, but immediately following this injury the strabismus returned to as severe a degree as before. Following general improvement the strabismus again improved to about 80 per cent. This may be of interest along the line of injuries of the cranial nerves.

Dr. Stone: Dr. Skoog mentioned injury of the cranial nerves. I think the reason that most of the patients in my series recovered was because the injury did not affect the nerve tissue. If there had been tearing I am sure they would not have recovered.

# Book Reviews

"Kinésie Paradoxale" des Parkinsoniens. Contribution a l'étude du mecanisme de la motilité volontaire. (Travail du service du docteur Babinski). By Dr. J. Jarkowski. Price, 12 francs. Pp. 78. Paris: Masson & Cie, 1925.

After an interesting description and discussion of many cases, the author advances an original conception of the mechanism of voluntary motor activity. "Kinésie paradoxale," commonly observed in Parkinson's syndrome, has never received sufficient attention from neurologists. All theories that are offered to explain the mechanism of motor trouble in Parkinson's disease, which fail to explain the phenomenon of paradoxic kinesis, must be considered as unsatisfactory. The author's conception can be summarized as follows:

1. Voluntary motility is the result of collaboration of two functionally opposed motor systems: (*a*) expansive system (système expansif), through which the individual takes part in the external world, and (*b*) executive system (système executif ou frenateur) inhibiting the first, and having for its function the learned motor acts — execution of isolated movements for definite purposes. The first system bears on the quantitative aspect of motor activity. Its lesion does not produce paralysis, but lack of movement (akinesis — Parkinson's syndrome). The second bears on the qualitative aspect of motor activity. Deficiency of the executive system does not produce abolition of movement — the crude reflex movements even become exaggerated — but it becomes impossible to accomplish isolated acts (pyramidal syndromes).

2. The author distinguishes two groups of reflexes: (*a*) segmental reflexes (tendinous, cutaneous reflexes of defense, etc.), confined to a limited part of the body and beyond voluntary control; (*b*) synthetic reflexes ("réflexes hyperalgésiques, réflexes à la surprise," etc.), in which the organism reacts as a whole, and which are intimately associated with the affective, emotional and psychic state of the individual. The last group of reflexes compares with those phenomena which were described by Sherrington in decerebrated animals as "pseudo-affective" reflexes. The author agrees with the observation of physiologists, but thinks that the attribute "pseudo" is not justified, because the fact that the cortex is eliminated does not mean that nothing psychic is left below it. Camus obtained distinctly psychic phenomena in animals by stimulating the base of the brain. Orzechowski justly pointed out that the striate body is intimately associated with the personality of the individual, and that one of the most striking features of extrapyramidal diseases (Parkinson's disease, Wilson's disease, pseudosclerosis, choreas) is that they involve largely the sphere of psychic manifestations. Therefore, the author regards these reflexes as affectivomotor reactions ("reactions affectivo-motrices"). Subcortical nuclei of the brain (thalamus, striopallidum, corpus Luysi, substantia nigra) are the seat of the central apparatus of these reactions. The cortex and pyramidal system inhibit these reactions, so that they become exaggerated in hemiplegia, and in Brown-Séquard's syndrome (hyperalgesic reactions); on the contrary, when the center of these reflexes is affected, as in Parkinson's syndrome, the reactions are diminished or abolished.

3. The author, a few years ago, described a clinical phenomenon which he called "reaction of antagonists"; this consists of reflex contraction of a muscle following the displacement of a segment of the limb in a direction opposite to

the motor effect of this muscle. The reaction is a true reflex and has its central apparatus probably in the cerebellum (Babinski). The author admits that, besides the cerebellum, the pyramidal system takes part in the production of this phenomenon (C. Vogt). In parkinsonian rigidity, the reaction of antagonists is exaggerated (uncontrolled cerebellum). The author feels that the rigidity itself is the result of summation of a series of infinitesimal reflex contractions of antagonists accompanying the displacement of segments of the limbs in movement. The affectivomotor reactions and the reaction of antagonists are functionally opposed reflexes (antagonistic reflexes of Sherrington). Normally, the affectivomotor reflexes are stronger. They are the primum movens of voluntary motor activity, and their function is what the author calls "proto-energy." Proto-energy is the essence of every act, but the reactions that express it, "violent and blind," are likely to exceed their purpose; the system of control and of inhibition (cortex) interferes here. The voluntary motor activity is the result of proto-energy (expansive apparatus) and of the apparatus of control (executive apparatus). The essential trouble in Parkinson's disease is lack of the proto-energy (failure of affectivomotor reactions) from which results a diminution of the impulse to perform an act, an apparent apathy and a difficulty of effort. This, altogether, gives the picture of akinesis. Akinesis, therefore, has nothing paradoxic in it; it is the essential manifestation of this disease and, with progress of it, can lead to complete inactivity of the individual. The deficient function of the expansive apparatus opposed to the apparatus of inhibition produces the exaggeration of function of antagonists. Parkinsonian rigidity, which therefore is a secondary trouble, can be inhibited whenever it receives a discharge of remaining proto-energy sufficient to counteract the excessive influence of the opposed centers (cortex-cerebellum), e. g., under the influence either of a sufficiently strong external excitation or of an accidental impulsive association. This is the explanation of the phenomena of "kinésie paradoxale."

HERZKRANKHEITEN UND PSYCHOSEN. (PSYCHOSES ASSOCIATED WITH HEART DISEASES). EINE KLINISCHE STUDIE. By E. LEYSER. Volume 25 of the "Abhandlungen aus der Neurologie, Psychiatrie und ihren Grenzgebieten, Beihefte zur Monatsschrift für Psychiatrie und Neurologie" edited by K. BONHOEFFER. Price, 4 marks. Paper. Pp. 84. Berlin: S. Karger, 1924.

After comments on the rarity of material suitable for this study and on the difficulty of distinguishing between features that are caused by the heart disease and those that belong to the make-up of the patient, Leyser presents a series of cases arranged in three groups: psychoses with heart disease uncomplicated by other conditions that might lead to neuropsychic disturbances; psychoses with heart disease complicated by cerebral arteriosclerosis and other disease conditions, and psychoses in which the heart disease is a complicating factor.

Disturbances in heart function may give rise to two kinds of mental disorder: In the first group are syndromes caused by the unknown noxae that are produced by the heart disease — manic and depressive moods, stupor, delirium, hyperkineses, twilight states, hallucinoses and confusion—all of them heteronomous symptom-complexes or exogenous reaction types in the sense of Bonhoeffer, with the possible exception of depression. When homonomous syndromes are combined with the heteronomous, the former are usually present during the onset and subsidence of the psychosis, the latter filling up the interval. It is suggested that the homonomous features are determined by the constitution of the patient, whereas the heteronomous manifestations are brought

about by direct injury to the brain. Individual differences in the heteronomous syndromes that do not depend on the state of the consciousness seem to be related more to the particular region of the brain affected than to the constitution of the patient.

Little is known of the nature of the noxae; they are independent of the formation or absorption of edema of the body. For the development of a cardiogenic psychosis, however, something is needed in addition to the noxae, something that seems to be in the nature of a suitable soil, though this point needs extended investigation. Neither arteriosclerosis nor other destructive brain processes seem to favor the development of the cardiogenic psychoses; infections and intoxications, also, seem to be without influence, as is suggested by the fact that no cases could be found for making such a study. Only one constitutional type — the "autochthonously labile" — in the material studied seemed to have had such an influence; no such relation was observed with the "reactively labile" or epileptic types.

The second group of symptoms are the anxiety states of varying degrees of severity, which are related to the sensations of palpitation and air hunger caused by the heart disease, though there is also involved a psychogenic (or better, "thymogenic") factor. For the development of the anxiety states, clearness of consciousness and intactness of the personality are necessary; they are common preceding the development of a cardiogenic psychosis. In defect psychoses and schizophrenic states with marked destruction of the personality, the thymoplastic power of the cardiac sensations is lost, though purely somatogenic psychoses may still be brought about by the noxae of the heart disease.

The abstracts given indicate the scope of the work. The material is excellently and conservatively presented, serving perhaps more to suggest lines of research than to establish definite conclusions, and the monograph can be heartily recommended to all who are interested in the scientific study of psychiatry.

THE SURGICAL TREATMENT OF GOITER. By WILLARD BARTLETT, A. B., A.M., M.D., D.Sc., F.A.C.S. With Foreword by DR. CHARLES H. MAYO. Price, $8.50. Pp. 365, with 130 Original Illustrations. St. Louis: C. V. Mosby Company, 1926.

This excellent monograph of 358 pages concerning the surgical treatment of the thyroid gland is especially to be recommended to the young surgeon. It presents to him in a clear, concise manner the history and development of this branch of surgery, and leaves him with a well defined picture of the present status of knowledge and the operative procedure in the best thyroid clinics.

Starting with an interesting foreword of approbation by Dr. Charles H. Mayo, the book proceeds in an interesting and readable manner through the history of thyroid pathology and surgery, the indications for surgical intervention and all the details of surgical treatment. The author's outstanding plea is for individualization. Each patient is a separate problem with infinitely variant factors and cannot be treated properly by "rule of thumb." Throughout the clinical part, the author's cases are liberally used in illustration, even though they expose his own errors. The chapter on pathology is written by Louis B. Wilson of the Mayo Clinic and that on associated cardiac conditions by Samuel B. Grant of St. Louis.

The book will be of interest and value principally to the surgeon, especially to the developing surgeon, but it may be read with enjoyment and advantage by all interested in this field of medicine. Preoperative and postoperative care

of the patient are dwelt on, and attention is called to the increased tolerance of the hypermetabolic patient for various drugs, particularly opiates and hypnotics. Neurologists and laryngologists particularly will be interested in the chapter on laryngeal complications written by French K. Hansel of St. Louis. A full bibliography terminates each chapter of this unusually meritorious work.

A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. By Percival Bailey and Harvey Cushing. Price, $5.00. Pp. 175, with one hundred and eight illustrations. Philadelphia: J. B. Lippincott Company, 1926.

This little book is an attempt to bring "some order out of chaos" in the study of "tumors that are commonly grouped together as gliomas." It is an elaboration of the work that has come out of the Cushing clinic within the last few years. The variations in the clinical pictures in gliomas are well known; the wide differences in the histologic structure and even the gross appearance of these tumors have puzzled all who have had occasion to study them. In this book an effort is made to trace back the histologic structure to embryologic type or types. Twenty different cell types are recognized with fourteen different types of tumors, as follows: medullo-epithelioma; medulloblastoma; pineoblastoma; pinealoma; ependymoma; neuro-epithelioma, spongioblastoma: (*a*) multiforme and (*b*) unipolare; astroblastoma, astrocytoma: (*a*) protoplasmaticum and (*b*) fibrillare; oligodendroglioma; neuroblastoma; ganglioneuroma, and papilloma chorioideum.

The chapter on histologic methods is too brief, especially for those who are not acquainted with the newer technical methods.

The authors are to be congratulated on this excellent little book. It marks a distinct advance in the study of gliomatous tumors and blazes a path for the eventual full recognition of the entire glioma group.

The Human Cerebrospinal Fluid. An Investigation of the Most Recent Advances, as Reported by the Association for Research in Nervous and Mental Disease. The Proceedings of the Association, New York, Dec. 29 and 30, 1924. Price, $10.00. Pp. 568. New York: Paul B. Hoeber, Inc., 1924.

This volume represents the fourth publication of the Association for Research in Nervous and Mental Disease. The following statement from the preface expresses briefly the scope of this volume: "The clinical contributions which appear in this volume are based upon over five thousand recorded examinations of the human cerebrospinal fluid obtained from all conceivable pathological states, and represent almost all known clinical conditions. The section of the book concerned with the normal characteristics of the human cerebrospinal fluid has been included in order that this book may not only be a record of present-day research and investigation, but also that it may be of value as a standard reference volume." Many of the articles appeared originally in the Archives of Neurology and Psychiatry. The work represented reflects credit on the organization. It is to be hoped that the association will continue in its purpose, and that it will receive the continued support that it merits.

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